EXHIBIT B

Report Prepared for Blackwell Burke

In re Bair Hugger Forced Air Warming Devices Products Liability Litigation

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I. Anesthesia, cooling body temperatures (hypothermia) and the associated adverse events

The normal body temperature in healthy people is 98.6° F or 37° C. There is little fluctuation during the day because of the body's sophisticated thermostat, located in the brain, which maintains a relatively constant temperature. This is good because the body's chemistry works best at 37 ° C.

Hypothermia is defined at <36 ° C (< 96.8° F), when measured in deep tissue ("core" temperature). With anesthesia the body's core temperature (chest, abdomen, brain and spinal cord) drops, and there is a failure of the thermostat's regulation to normalize the temperature (red line in figure 1).

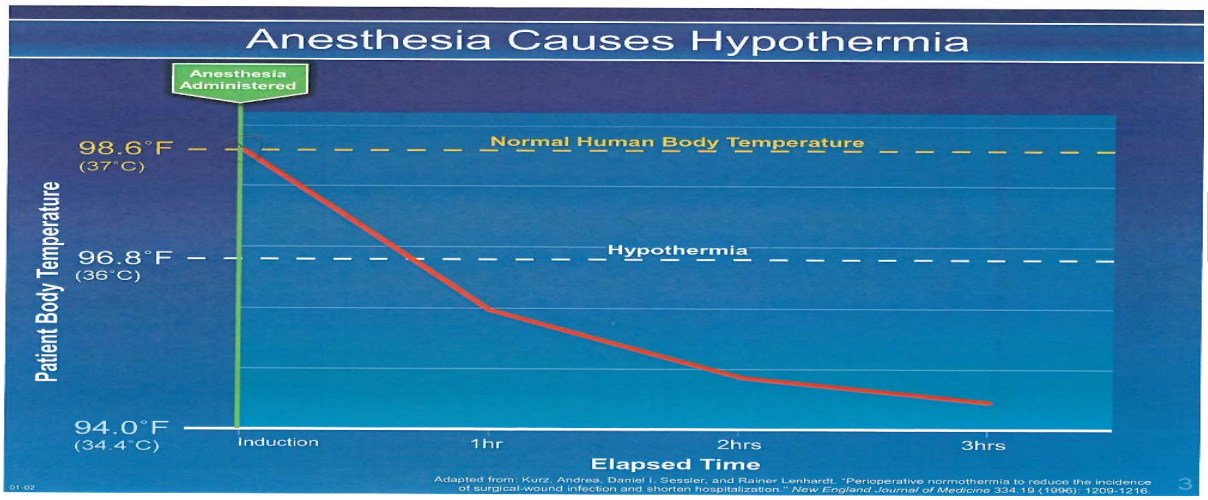
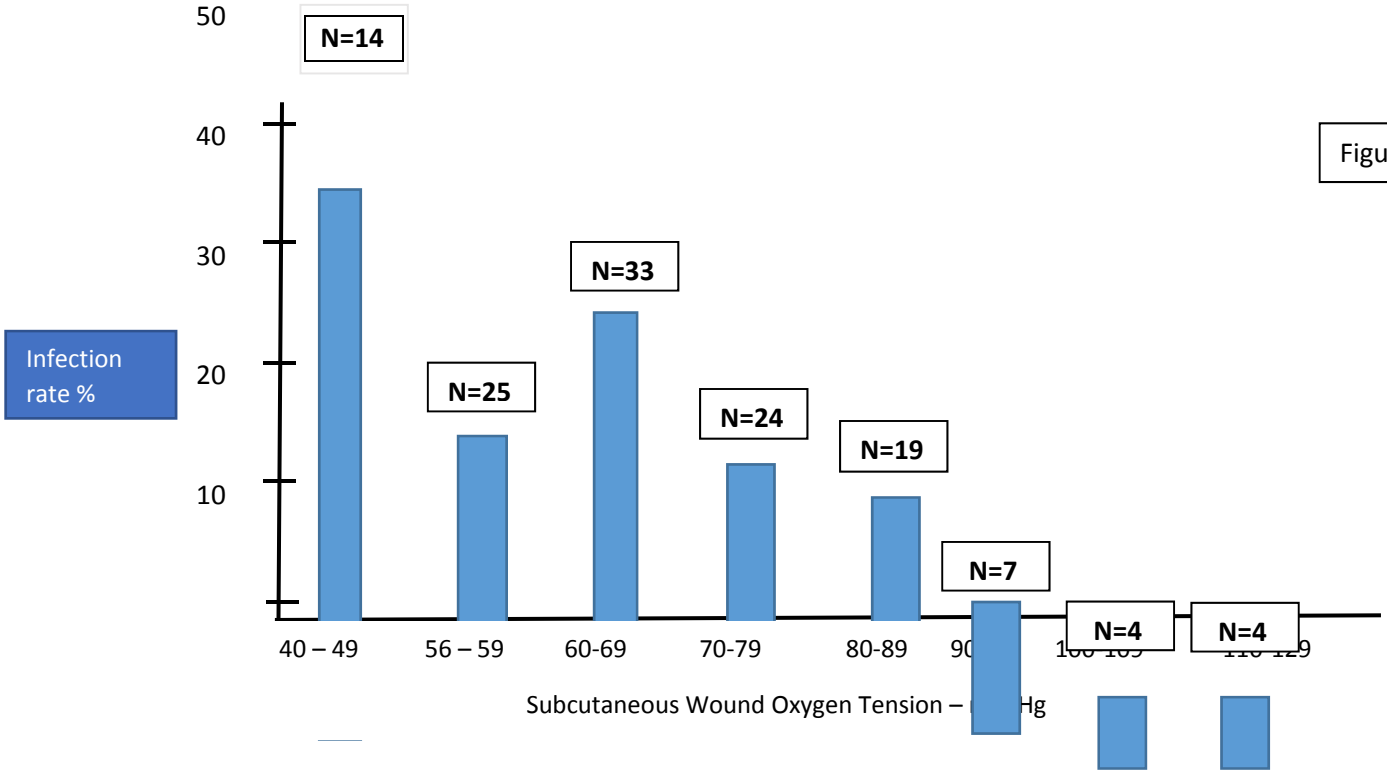


Figure 1

The body's response to the stress of hypothermia is an outpouring of the stress hormone, norepinephrine, causing constriction of the arterial blood supply to the subcutaneous tissue (just below the skin), essentially a decrease in blood perfusion right at the operative site. The reduced blood supply in turn means that there is a reduced oxygen tension at the subcutaneous area, and a resulting sluggish response of white cells responding to nearby bacteria, to their engulfment of the bacteria, and to their killing of bacteria. Furthermore, the perioperative antibiotics - administered to reduce the risk of a surgical site infection - do not work as well in lower oxygen states. (Hart S. R. et al. Unintended perioperative hypothermia. *The Ochsner Journal* 2011; 11: 259-70; Kasai T et al. Preoperative blood pressure and catecholamines related to hypothermia during general anesthesia. *Acta Anesthesial Scand* 2003; 47: 208 – 12; Sesssler D.I. et al. Non-Pharmacologic prevention of surgical wound infection. *Anesthesial Clin* 2006; 24: 279-97).

The physiological response to hypothermia has been linked to important outcomes in surgical patients. Clinical studies have shown that the lower the oxygen tension of the subcutaneous tissue, the greater the surgical site infection risk. In a prospective observational study of 130 surgical patients, Harriet Williams Hopf and colleagues showed an inverse relationship between subcutaneous wound oxygen tension and surgical site infection rate (Figure 2): if the oxygen tension was as low as 40-49 mm Hg, the infection rate was over 40%, but the SSI rate fell to zero if the oxygen tension was $\geq$90 mm Hg. (Hopf et. Al, Wound Tissue Oxygen Tension Predicts the Risk of Wound Infection in Surgical Patients, Arch Surg 1997, 32:997-1004)



Infection rate is inversely proportional to maximum subcutaneous wound oxygen tension (Psq O2 max) ($p < 0.01$, X2 contingency table)

Hopf, et a.l Arch Surg 1997; 132:997-1004

This figure shows the high proportion of general surgery patients whose subcutaneous wound oxygen tension was low and who were at risk for a SSI in the pre-warming era. Hypothermia during surgery has not only been linked to increased risk of wound infection but also increased risk of morbid cardiac events, a need for more blood transfusions, complications of major surgery and post-operative shivering (Eileen Scott. A systematic review of intraoperative warming to prevent post-operative complications. AORN Journal 2006; 83: 1090 – 1113).

The CDC classifies wound infections as “superficial” if they involve skin and subcutaneous tissue and “deep” if they involve “fascia or muscle”. An organ/space SSI involves any part of the body deeper than facial muscle and was opened or manipulated during the operative procedure.

Post-operative pain has also been linked to elevated stress hormone levels’ associated arteriolar vasoconstriction, and decreased tissue oxygen pressure. Akca and colleagues hypothesized that patients undergoing knee surgery would have less pain and higher subcutaneous tissue oxygen levels if the knee was injected at the end of surgery with lidocaine vs saline. 30 adult patients were randomized, and over the following hour and a half, the placebo group had a mean subcutaneous oxygen level of 86 mmHg vs 113mm in the lidocaine group ($p=0.016$), and the mean pain score (on a 1-100 visual analogue) was 40 in the placebo group vs 11 in the lidocaine group ($p < 0.001$). The authors suggest that “control of postoperative pain is a major determinant of surgical site infection,” citing the work of Hopf et al. (See Akca et al., Postoperative pain and subcutaneous oxygen tension. *Lancet*. 1999; 354: 41-42).

Both studies are consistent with the concept that stress from anesthesia or of pain is linked to reduced subcutaneous oxygen pressures, known to influence surgical site infection rates. Furthermore,

warming increases subcutaneous oxygen tension: Ikeda and colleagues used a radiant heater applied locally to 10 volunteers and measured subcutaneous oxygen tension. At 38° C, 42°C and 46°C, oxygen tension increased approximately 50% during heating to comparable levels at all three temperatures tested. Of interest, subcutaneous oxygen tension remained elevated for 3 hours after heating was discontinued. (Ikeda et al., Local Radiant Heating Increases Subcutaneous Oxygen Tension, *Am J Surg* 1998; 175: 33-37)

II. Benefits of avoiding hypothermia, Forced Air Warming and the Bair Hugger Device

Fortunately the adverse events linked to anesthesia, the associated hypothermia and reduced tissue oxygenation can be reversed with warming of the surgical patient, maintaining a core body temperature greater than 36° C (96.8° F). Most studies have been performed with forced air warming devices and most of the latter with the Bair Hugger.

a. Prospective, Randomized, Controlled Clinical Trials

i. Andrea Kurz and colleagues randomized 200 colorectal surgery patients to the use of a Bair Hugger patient warming system during the operation or to control (no warming). The controls had a forced air warmer set to deliver ambient air vs a 40° set point for the warmed group, which also received IV fluids through a warmer. Core temperatures at the end of surgery were significantly lower in controls (34.7 ± 0.6° C) vs the warmed group (36.6 ± 0.5° C). Hospital stay in the infected patients was one week longer than the unifected... "indicating that most infections were substantial." To minimize the decrease in wound perfusion due to pain postoperatively, patients with pain were given opioids. **The surgical site infection rate was 19% in controls vs 6% in the warmed patients.** (Kurz et al., Perioperative Normothermia to Reduce the Incidence of Surgical-Wound Infection and Shorten Hospitalization, *N Engl. J Med* 1996; 19:1209-1216).

In her deposition, Dr. Andrea Kurz was asked if she still thought the data were valid and also if she were to do the study again, what changes would she make? She said that she still believes that "maintenance of normothermia decreases infection risk, but the effect might be closer to 30% reduction or so, which in effect is a humongous, enormously large effect size for any medical intervention" (p. 201). She also said that today she would have a larger study size and emphasized that the control arm would have to be warmed in some fashion for an ethically sound study since "active warming has become standard" (p. 199). The key point is that "due to the fact that patients are warmed, we don't see the significant decrease of hypothermia any more, and therefore in any study the effect size wouldn't be as large as in this particular one" (p. 199).

ii. Andrew Melling and colleagues randomized 421 patients undergoing clean surgery to ≥ 30 minutes of preoperative warming or no warming. All patients were expected to have brief operative times of under 50 minutes. Both Bair Hugger and local warming methods increased core temperatures by .35 and .13° C and had equal outcomes, and their results were pooled and compared to controls with no warming. The mean core temperature after surgery was > 36° C. **The surgical site infection rate was 14% in controls and 5% in warmed patients** (Melling et al., Effects of perioperative warming on the incidence of wound infection after clean surgery: a randomized controlled trial, *Lancet* 2001; 358:876-80).

Both clinical trials used the Bair Hugger and had blinded (masked) evaluators who did not know to which study arm the patients were assigned.

b. *Systematic reviews of controlled clinical trials (meta-analyses).*

Meta-analyses are systematic reviews of ≥ 2 studies, performed to estimate the overall effect of an intervention, since any single study may have a somewhat different outcome than another. Meta-analyses represent the best overall estimate of the intervention.

A meta-analysis was reported by the Cochrane Library in 2016. They included both the Kurz and Melling studies and **estimated the risk ratio for surgical site infections favoring warming at 0.36 (CI_{95} - 0.20-.66), suggesting that 64% of surgical site infections could be eliminated with warming.** (Madrid E et al. Active body surface warming systems for preventing complications caused by inadvertent perioperative hypothermia in adults (Review). (Cochrane database of systematic reviews 2016, Issue 4. Art No.:CD009016. Doi: 10.1002/14651858. CD 009016.pub 2.) The authors rate the evidence as low to moderate and conclude that "forced air warming (FAW), applied in the surgical pre-or intraoperative phases or both, seems to have a beneficial effect in terms of a lower rate of surgical site infections and complications, at least in people undergoing abdominal surgery.."

In a response to concerns about safety, any increased risk of SSIs with forced air warming systems – the Bair Hugger, ECRI issued a report in 2013. After a critical review of the literature. The ECRI Institute, an independent review body with skills in evaluating data, found no sufficient evidence linking forced air warming to surgical site infections. (Health Devices April 2013 pp 122-125. www.ecri.org).

c. *Historical Cohort Studies*

Five historical studies have been reported to examine surgical site infections. These are important, "real-world" data to examine effectiveness of warming systems in actual practice. All five studies used forced air warming systems, and 4 of 5 warming systems were with the Bair Hugger. In one study, the rates of all infections, cardiac events, and mortality were also examined. Each asked the question, after the use of a forced air warming device, if patients avoided hypothermia, were the outcomes the same as or different from those who developed unwanted hypothermia? (See data in table below). A more recent 6th retrospective cohort study examined 4 different definitions of hypothermia to examine links to surgical site infections.

Study	Country, Device Reference	No. Patients and type if Surgery	Percent under 36^0 C	Outcomes (Risk Ratios) SSI	All Inf.	Morbid Cardiac Events	Mortality
1.	U.S. Warm Touch set @ 43°C *Anesth* 2015; 123: 116-25	46,683 General Sgy	3%	.86 N.S. Trend	.68* *Significant, favoring warming	.60*	.41*
2.	Holland **Bair Hugger** *J Arthroplasty* 2013; 28:895-9	THA* – 415 TKA *– 257	27%	Surgical Site Infections RR if cool 3.7 p=0.061	1% if warmed vs 3.7% if hypothermic		
3.	Japan **Bair Hugger** set @ 38° C *Surgical Infect* 2016 Doi: 10.10. 1089/Sur.2015. 182	1409 High risk GI patients. ~ half with cancer	37.5%	RR = 1.0 if severe hypothermia (<35° C) Normothermia Mild Hypothermia			Infection rate 33.3% 19.2% 17%
4.	U.S. **Bair Hugger** Orthopedics 2016 39:e1170-77	1525 Orthopedic patients with hip fractures	17%	Multi-variable logistic regression for deep SSI: OR 3.30 (1.19 – 9.14) p=0.022			
5.	U.S. **Bair Hugger** Frisch NB et al Orthopedics 2017; 40:53-63	THA and TKA (N=2397)	44% 33%	1% if warmed 1% if not warmed			

* THA stand for total hip arthroplasty (replacement)
* TKA stands for total knee arthroplasty (replacement)

Inf = infections
N.S. = not significant

1. **The 2015 U.S. study at Hopkins showed a 3.7 – fold non-significant trend towards reducing SSIs but showed significant reductions of total infections, of morbid cardiac events, and deaths within 30 days.**

2. **The Dutch study of THA and TKA showed a benefit with warming at a borderline P value of 0.061. No clinician would ignore these beneficial findings in hip and knee arthroplasty patients.**

3. **The Japanese study showed no overall effect but an important reduction in patients with normothemia vs severe (<35°C) hypothermia in very ill patients.**

4. **The U.S. hip fracture study is the first and largest study analyzing the effect of intraoperative hypothermia in orthopedic patients. It showed a large protective effect if patients remained warm.**

5. **The U.S. study of THA and TKA showed no difference in warmed vs not warmed patients in terms of SSIs.**

In general, the studies show the benefits of warming. Four of the five used a Bair Hugger warming device, three studied orthopedic patients and two of the studies focused on patients with THA or TKA.

Very recently, Rebeccah Baucom and colleagues in a 6th retrospective cohort study used 4 different definitions of hypothermia to examine any link of hypothermia to SSI: temperature nadir, mean intraoperative temperature, percentage of time at the temperature nadir and percentage of time with a temperature of less than 36°C. The adjusted odds ratio, respectively, for the 4 metrics of hypothermia were 0.96 (.75-1.22). 1.10 (0.60 – 2:00); 1.02 (0.90 – 1.16) and 1.17 (0.76 – 1. 1.81). Thus, very small non-significant odds ratios linking infection to hypothermia were noted for 3 of the 4 definitions of hypothermia. (R.B. Baucom et al., Association of Perioperative Hypothermia during Colectomy with Surgical Site Infection. JAMA Surg 2015; 150: 570-5).

It has now been shown that pre-operative warming of surgical patients plus intraoperative warming has benefit over intraoperative warming alone. (Andrzejowski J et al., Effects of prewarming on post-induction core temperature and the incidence of inadvertent perioperative hypothermia in patients undergoing general anesthesia. Brit J Anaesth 2008; 101:627-51). In a study of 68 patients undergoing spinal surgery, 31 were prewarmed, and 37 controls were without prewarming. Both groups had operative warming with the Bair Hugger. A smaller decease in mean core temperature was noted in the prewarmed group at 40, 60 and 80 minutes after induction ($p<0.05$). The AUC (area under the curve) of the prewarmed group was greater during the procedures than the controls ($p<0.005$). Any comparison of warming systems should take into account the concurrent use of prewarming systems.

d. *Case Control Study*

Recently Brown and colleagues from the Mayo Clinic reported data from a retrospective case control study examining the relationship of SSI to intraoperative hypothermia in patients undergoing clean surgery. The 10 year study involved 1335 patients with a SSI and 3683 controls. The authors examined the relationship of SSIs with composite SCIP – 10 compliance [surgical care improvement project that seeks a goal of normothermia] (AOR 0.89; CI_{95} . 63 – 1.24); with temperature compliance ($\geq$ 36° C) (AOR .92: CI_{95} .78 – 1.09); and forced air warming device documented (AOR.95: CI_{95} .76 - 1.19). None of the studies showed harm in the overall analyses. All adjusted odds ratios (AOR) were less than 1.0, suggesting a trend for fewer SSIs with warming compliance. None were statistically significant.

In further subset analyses (in their Table 4), there appeared to be a higher risk for SSI in general surgery patients, reduced risk in Neurosurgery patients, and trends for lower SSI rates if SCIP – 10 compliance was met for orthopedics, spine and vascular surgery patients. (Brown MJ et al. Intraoperative hypothermia and surgical site infections in patients with class 1/clean wounds: A case control study. J Am Coll Surg. doi: 10.1016/J. JAM Coll Surg. 2016. 10.050). It is of interest that the Mayo Clinic continues to use the Bair Hugger for surgery.

It should be noted that the Brown study (2016) was 20 years after the Kurz study (1996), 15 years after the Melling study (2001), and six years after the Darouiche study (2010) showing 40% reduction in SSIs with a switch from povidone-iodine to chlorhexidine alcohol skin preps.

It is likely that with increasingly successful efforts over time at controlling the microbiome and other risk factors for SSI, the residual modifiable factors were reduced, and study power to show a significant difference was low. The authors agree: "It is possible that these other measures at reducing SSI obscured any effect of perioperative hypothermia avoidance."

In summary, the benefits of warming are established and linked to reduced risk of SSIs. The Bair Hugger is established as an effective method of maintaining normothermia.

e. *National data in the U.S. in the era of the Bair Hugger.*

Trends in In-Hospital Major Morbidity and Infections after Total Joint Arthroplasty: United States 1998-2008 – The increasing trends of comorbidity in U.S. patients. The manuscript by Kirksey et al *Anesth Anal* 2012; 115: 321-7 showed the following:

i. *The need to correct for rising comorbidities in the U.S.*

During the 1998-2008 study period, the number of total knee and total hip arthroplasties performed in the U.S. increased linearly (144% for TKA and 79% for THA); and by 2008, there were 616,000 TKA and 277,400 THA – thus twice as many knee as hip operations. Importantly, **the comorbidity burden (burden of underlying diseases) increased significantly over the study period** and was associated with postoperative complications including sepsis. Specifically, the comorbidity burden increased 35% for TKA and 30% for THA patients over the decade. The incidence density of sepsis after THA increased from approximately 2 to 2.5 per

1000 hospital days over the decade. Of note, increases in sepsis were linked to increases in the comorbidy index. The term "sepsis" is not equivalent to prosthetic joint infections and includes pneumonia, urinary tract infection, bloodstream infection, sinusitis and other infections.
The authors concluded that **"the number of THAs and TKAs performed in the United States is rapidly increasing in an increasingly comorbidity – ridden population."**

ii. *National Data Corrected for Comorbidities*
The data by Kirksey et al were confirmed in an analysis of the Mayo Clinic Total Joint Registry (1993-2005) known to have similar characteristics to the national U.S. cohort – see Sing JA and Lewallen D.G. Increasing Obesity and Comorbidity in Patients Undergoing Primary Total Hip Arthroplasty in the U.S.: A 13 year study of time trends. BMC Musculoskeletal Disorders 2014; 15:441. doi: 10.1186/1471 – 2474-15-441.

In multivariate analyses, compared to 1993-5, significantly more patients in 2003-5 had BMI $\geq$ 40 (OR 2.79 – CI_{95} 1.85 – 4.22); Deyo – Charlson comorbidity index $\geq$ 3 (OR 1.32; CI_{95} 1.07 – 1.63); depression (OR 2.25 – CI_{95} 1.66 – 3.05); and anxiety (OR 1.71 – CI_{95} 1.19 – 2.15). Thus, the odds of being morbidly obese or having many comorbidities were ~ 3 fold more common in 2003 – 5 vs 1993 – 5; and the odds of being depressed or having anxiety were ~ 2 fold more common in 2003 – 5 among joint replacement patients.
The authors concluded that **"studies of THA outcomes should take these rapidly changing patient characters into account."**

iii. *Corroborating Data on Comorbidity Rises in the U.S.*
In 1990, obese adults comprised less than 15% of the population in the U.S. states. By 2010, 36 states had obesity rates of $\geq$ 25%, and 12 of the 36 states had rates of $\geq$30%. **Current data show that 36% of U.S. adults are obese.**
CDC. Overweight and Obesity: Adult obesity facts
Flegal KM et al. Prevalence of obesity and trends in the distribution of body mass index among U.S. adults, 1999 – 2010. *JAMA* 2012; 307: 491-7.

The prevalence of diabetes mellitus (DM) has been increasing all over the world. A 2011 CDC report estimated that DM affected ~ 25.8 million people in the U.S. (7.8% of the population) in 2010, of which 90 – 95% are type 2. Obesity contributed to ~ 55% of cases of diabetes mellitus. Dept HHS. CDC, 2010. National diabetes fact sheet: National estimates and general information on diabetes and prediabetes in the U.S. http://www.cdc.gov/diabetes/pubs/pdf/ndfs - 2011.pdf. (Prevalence of overweight and obesity among adults with diagnosed diabetes United States, 1984-1994 and 1999-2000. CDC (November 2004) mmwr.mmwr; 5 (45): 1066 – 1068).

A more recent study shows that the trends for physician diagnosed diabetes mellitus in the U.S. rose from ~ 5% to 12% between 1988-94 and 2005 – 2010. (Mozaffarian D et al, Heart Disease and Stroke Statistics – 2016 Update, A Report From the American Heart Association, *Circulation* 2015; 131: e29 – e322.)

In addition to an increased rate of carriage of *S. aureus* in obese surgical patients, another factor linking obesity to elevated SSI risk is subcutaneous tissue penetration of perioperative antibiotics. The pharmacokinetics and tissue penetration of cefoxitin in obesity has been studied by Toma, et al. and colleagues (See Toma et al., Pharmacokinetics and Tissue Penetration of Cefoxiting in Obesity: Implications for Risk of Surgical Site Infection, *Anesthesia & Analgesia*, 2011; 113:730-7).

Obese patients (N=14) were given 2 Grams of Cefoxitin preoperatively and subcutaneous levels were compared to healthy volunteers (N=11) and nonobese patients (N=2). Subcutaneous tissue concentrations were similar in the normal – weight healthy volunteers given only 1 Gram of Cefoxitin and the normal weight patients. In contrast, the subcutaneous concentrations in obese patients given 2 Grams of Cefoxitin were lower than those in the normal – weight subjects receiving 1 Gram and were approximately half those of the normal-weight subjects.

Since approximately 68 % of American adults are overweight (BMI ≥25 Kg/M^2), 33% are obese (BMI > 30) and 6% obese (BMI ≥30) and 6% morbidly obese (BMI ≥ 40), the risk factor of obesity for SSI is a huge problem among patients undergoing surgery (Flegal et al., Prevalence and Trends in Obesity Among US Adults, 199-2008 JAMA 2010; 303: 235-41).

The point about comorbidities, e.g. obesity and diabetes, is that they increase the risk of a surgical site infection. Thus, crude rates may be expected to increase over time if comorbidity frequency increases. To maintain a level playing field and look at true changes over time, the effect of the comorbidities needs to be considered. By analogy to the financial world, to examine the value of a dollar over time, one has to correct for inflation over that period.

iv. Revisions of THA Over Time

The manuscripts by Kurtz et al. and by Cram et al. show the following:

- From 1990 to 2002 the number of revision procedures almost doubled for hip surgeries [tripled for knee surgeries]. (See Kurtz et al., Prevalence of Primary and Revision Total Hip and Knee Arthroplasty in the United States From 1990 Through 2002, *J. Bone Joint Surg Am.,* 87:1487-97, 2005)
- Revisions for total hip replacements constitutes ~ 20% of the volume of primary total hip replacements. (See Cram et al., Total Knee Arthroplasty Volume, Utilization, and Outcomes Among Medicare Beneficiaries, 1991-2010, *JAMA* 2012; 308:1227-36).

Infection rates are higher after revisions than for primary THA or TKA. Thus, when examining trends in infection rates, it is also important to separate the THA primary procedures and TKA primary procedures from combined THA and TKA data that also include revisions.

v. Notes on THA-Associated Infections and Sales of Bair Hugger Devices: United States

- Over time the number of THA and TKA and revisions increased.
- The increases in orthopedic operations for these procedures occurred in an increasingly comorbid patient population.
- Increases in sepsis over time were linked to increased comorbidity over time.

- Bair Hugger sales increased over time as hospitals chose to use the device for the increasing number of patients having surgery for THA and TKA and revisions of both.
- National data on THA show that between 1998 and 2008, infection rates increased from 2 to 2.5/1000 patient days.
- Increases in infection rates are correlated with increases in underlying comorbidity burden. At the NIS website the authors state that over time there is more bias likely in the earlier periods than more recent periods. Such statements suggest under reporting of infection rates earlier than later. Such underreporting earlier would tend to show a spurious rise in infections (sepsis) over time.
- **No national data support causal link of Bair Hugger sales to infections after THA or TKA.**

vi. *National Data Corrected for Comorbidities*

In 2013, a group of orthopedic surgeons examined the question, has the rate of in-hospital infections after total joint arthroplasty decreased? (Rasouli, et al., Has the Rate of In-hospital Infections After Total Joint Arthroplasty Decreased?, Clin Orthop Relat Res (2013) 471: 3102-11). They examined the National Inpatient Sample (NIS) database from 2002 – 2010. The numbers of primary THA increased from 200,000 to just over 300,000 during the study period.

In examining the rates of prosthetic joint SSI over time, they used a measure of comorbidity (the Elixhauser Comorbidities) to correct for underlying illnesses. The overall rate of SSI during the period was 0.31%. UTI and SSI rates were both relatively flat over the period queried, but multivariate analysis indicates that **when other demographic and clinical factors were controlled for, both infection rates dropped over time. This appears to be the first use of a comorbidity index to correct for confounders known to increase the risk of a surgical site infection after joint arthroplasty.**

Thus, substantial rises in comorbidities have been reported by Kirksey et al, confirmed by Mayo Clinic data, and noted in U.S. trends for obesity and diabetes mellitus in several studies. When comorbidity is controlled – leveling the playing field over time – it has been reported that surgical site infection rates have fallen over time during the use of the Bair Hugger.

- More recently the Centers for Disease Control and Prevention released their national data. (See CDC National and State Healthcare Associated Infections Progress Report, Based on 2013 Data, Published January 2015). **In the report they utilized risk adjustment models to correct for procedure related risk factors.** For THA and for TKA, comparing 2013 to a 2008 baseline, they show a **27% reduction in surgical site infections over time for THA and a 40% reduction over time for TKA. These data confirm the data of Rasouli et al. in showing reduced trending rates of SSI after joint arthroplasty in the era of the Bair Hugger.**

So far, two favorable clinical trials data, the combined studies' estimates from a meta analysis data, six historical cohort studies, a case-control study, and the national trends of infection rates after primary THA and TKA corrected for comorbidities show no harm with forced air warming and the Bair Hugger specifically. They often show remarkable benefit.

f. Available microbiological data that show no signal for a link to SSIs from the Bair Hugger and provide biological plausibility for its non-risk.

Clinical studies surely have more weight than laboratory and other non-clinical studies for examining cause and effect relationships. Nevertheless, if any harm from the use of the Bair Hugger could be likely, one might expect to see suggestions from bacterial studies in a real or simulated operating room. On the other hand, if bacteriological studies showed no likely risk, they would in fact be further support for the favorable and more relevant clinical data.

Between 1991 and 2013 there have been eight studies attempting to determine if the Bair Hugger system increases viable bacteria at the surgical site or in the air of the operating room

Author/Ref	Key Design Points	Outcome
R.S.Zink et al Anesthesia and Analgesia 1993;76: 50-53	8 volunteers on an OR table Agar plates placed on abdomen for 4 hours: 2h with warmer and 2h with control	No difference in CFU noted on the Agar culture plates
A.C. Hall et al Poster Dec 9, 1991 Postgrad Assembly in *Anesthesia* (PGA) NY, NY	20 patients undergoing maxillofacial surgery randomized to: Bair Hugger (BH) or no Bair Hugger; culture plates in OR	BH: 7.35 CFU mean/plate No BH: 7.27 CFU mean/plate
J.K. Huang et al *Crit Care* 2003; 7.3: R 13	Air samples and wound specimens during 16 vascular surgery procedures using the Bair Hugger	A decrease in bacterial counts in air and around the patient after the use of the Bair Hugger
W.E. Dirkes et al *Anesthesiol* 1994 81: No 3A (Sept)	An agar plate of β-streptococci placed 10" from filter inlet; 2 warm air and 1 Bair Hugger. Air samples cultured.	No transmission in the air occurred of the streptococci during use of the Bair Hugger
B. Moretti et al *J Hospital Infect* 2009; 73: 58-63	Air samples during 30 THA (mean age 64 for patients); 3 different sampling sites. CFU counted/M^{-3}; means are illustrated	Empty Theatre: Site Mean CFU A1 17.8 A2 19.4 A3 19.2 Immediately after patient on table – before use: Site Mean CFU A1 79.2 A2 61.2

		A3 69.3 After Bair Hugger Site Mean CFU A1 41.7 A2 42.2 A3 42.2
M.S. Avidan et al *Anesthesia* 1997; 52: 1073-6	Experimental design in an empty OR; 9 Bair Huggers and 1 warm touch all convection warmers'; examine growth on agar plates	4/10 had growth if plates were directly in air steam 16" below the end of the hose. No growth, however, if warmers connected and blown through perforated blankets
L. Occhipinti et al Canad Vet J 2013; 54: 1157-9	Randomized study involving 100 canine surgeries; bacterial counts on surgical drapes counted before and after surgery	4/58 positive drapes afer Bair Hugger and 2/40 controls – no difference -
N. Tumia et al *J Hosp Infect* 2002; 52: 171 - 4	Air samples in 2 empty theatres and during 4 orthopedic operations (3 THA and 1 shoulder op.)	Non-significant rise in colony forming units (CFU) between empty theatre and warmer off and then a non-significant rise in CFU between warmer on and warmer off

In eight studies, 4 involved real patients, 1 was a veterinary study, and 3 involved simulated patients. **All the studies were small and overshadowed in causal inference by the clinical data reported above. Nevertheless, all microbiological outcomes showed no signal for risk vs controls.**

It should be noted that these publications between 1993 and 2013 were open and available to the public. These data stand in contrast to the unpublished, hidden data by Albrecht and others showing no increase in CFUs in various experiments with the Bair Hugger (see section vii b on particles, air bubbles, filter efficiency and cultures of the Bair Hugger apparatus). The unpublished data are further confirmation of the safety of the Bair Hugger.

More recently published data support the safety of the Bair Hugger (Oguz R et al. Airborne bacterial contamination during orthopedic surgery: A randomized controlled pilot trial: *J Clin Anesthesia* 2017; 38: 160-64). In that clinical trial 80 orthopedic patients were randomized to either forced air warming (Bair Hugger) or electric warming system (Hot Dog). The number of airborne bacteria was measured using sedimentation agar plates and nitrocellulose membranes at 6 standardized locations in the operating room. The authors report the following: In "multivariate analysis…the absence of unidirectional

turbulent free laminar airflow and longer duration of surgery increased bacterial counts significantly. The type of patient warming system and the number of health professionals had no significant influence on bacterial counts on any sampling site."

Summary – Benefits of avoiding hypothermia with use of forced air warming

Two clinical trials, one Meta-analysis, six historical cohort studies, one case control study, an independent review by the ECRI institute, two ecological national studies of prosthetic hip and knee infections in the Bair Hugger era, eight published microbiological studies, and seven unpublished and hidden microbiological studies of the Bair Hugger device are concordant with the conclusion that no harm results from use of forced air warming for surgical patients. A prospective clinical trial comparing the Bair Hugger vs the Hot Dog warming system showed no influence of either device on airborne colony forming units in the operating room. Almost all of the clinical studies employed the Bair Hugger warming system and several support a benefit, in fact, in reducing surgical site infections. No study shows harm with the Bair Hugger.

III. – Quality of the Data – Hierarchy in Ascribing Causal Relationships

In the hierarchy of studies designed to show evidence that one device is better than an alternative, prospective clinical trials are considered to have the highest quality and validity. These are prospective, controlled trials comparing one device to another in studies that are randomized and have blinded (masked) evaluation of critical end points. The studies have to be large enough to have an 80% statistical power to detect a clinically significant difference in the two systems if one exists. They are the gold standard for clinical decision making. If several small or large controlled clinical trials have been performed, a summary Meta-Analysis showing the average effect from all the data, can be performed.

In the absence of well-designed, large prospective clinical trials, large non randomized prospective cohorts showing a difference between one device vs another - examined concurrently - would be provocative and warrant a subsequent large clinical trial to show the relative value of the two systems being evaluated.

With respect to an alternative to the Bair Hugger, there has been no large prospective and controlled clinical trial showing a statistically significant improvement in outcome – a lower infection rate after surgery – with an alternative warming device.

There is no large controlled prospective cohort showing a statistically significant reduction in surgical site infection with use of an alternative to the Bair Hugger evaluated during the same study period.

There is also not a large retrospective trial - with concurrent use of both the Bair Hugger and HotDog device - suggesting a statistically significant reduction in surgical site infections with the use of an alternative to the Bair Hugger.

A single retrospective case-control study with many flaws suggested a better outcome with the Hot dog device than the Bair Hugger. The two devices were not compared concurrently, case finding methods were not described and many variables were not controlled. Only a univariate analysis was performed, and thus, the odds ratio reported is not supporting an independent predictor of infection. Several biases were present. See section VII C – The McGovern study.

At this point there are no compelling clinical data to show superiority of an alternative to the Bair Hugger for reducing surgical site infections. Specifically, no properly conducted clinical trial has shown that infection rates are significantly reduced with an alternative to the Bair Hugger. Current data do not show that an alternative to the Bair Hugger is safer than the Bair Hugger.

At the same time there are no compelling data to show that the Bair Hugger causes harm.

Hierarchy of Studies Designed to Show Evidence of Superiority of One Device to Another

1. Meta – analysis of several well conducted, prospective clinical trials that were controlled, randomized, and blinded (masked).
2. Single well conducted prospective clinical trial that was controlled, randomized and blinded (masked).

3. Large, well-designed prospective observational cohort studies with concurrent use of both devices and well defined case definitions and case finding methods with analyses that control for confounding variables.
4. Large, well-designed retrospective observational cohort studies with concurrent use of both devices and well defined case definitions and case finding methods with analyses that control for confounding variables.
5. Case-control studies in which the groups are analyzed retrospectively for risk factors for a specific outcome.
6. Cross sectional survey in which cases and controls are examined at specific moment in time. Better case control studies of alternative therapies are those in which the alternative options were used during the same study period. This approach controls for changes in other variables, that would not be corrected in before vs after retrospective studies.
7. Case series – a collection of cases that share a common time period or therapy; there is no effort to have concurrent controls or analyze for confounding variables.
8. Case reports.
9. Expert opinion.

   (See Greenhalgh T., How to read a paper Getting your bearings (deciding what eth paper is about, BMJ 1997, 315: 243-6)

Note: If no clinical studies are available to provide evidence, animal studies may provide clues which could be examined subsequently in human studies. If clinical data and no animal data exist, exploratory in vitro and other laboratory-based studies may be used to test initial hypotheses. Such studies would necessarily prompt better studies in the hierarchy of high quality methods for ascribing causal relationships. The outcome of interest, of course, should be SSIs comparing the Bair Hugger with an alternative warming device.

See graphics related to the Bair Hugger on pages 19 and 20 (Figures 2a – 2d).

2a. Hierarchy of Bair Hugger System Studies

Hierarchy of Bair Hugger System Studies

Clinical Studies: Gold Standard for Medical Research
Randomized studies examining impact of Bair Hugger system on rate of surgical site infections

Biological Plausibility Studies: Next best evidence
Studies of biologically plausible endpoints closely related to surgical site infections:

- Deposition of bacteria on wound site itself
- Movement of airborne bacteria

Exploratory Studies: lack clinical relevance and have no predictive value
Preliminary studies generally used to develop hypotheses for use in developing higher level studies

- Surrogate endpoints not correlated with surgical site infections, but inform whether biological plausibility studies are warranted
  - Movement of particles
  - Impact on airflow, non-mobilized bacteria
  - Heat differentials

31-01

2b. Clinical Studies

Clinical Studies

Clinical Studies explore impact of Bair Hugger system on surgical site infections

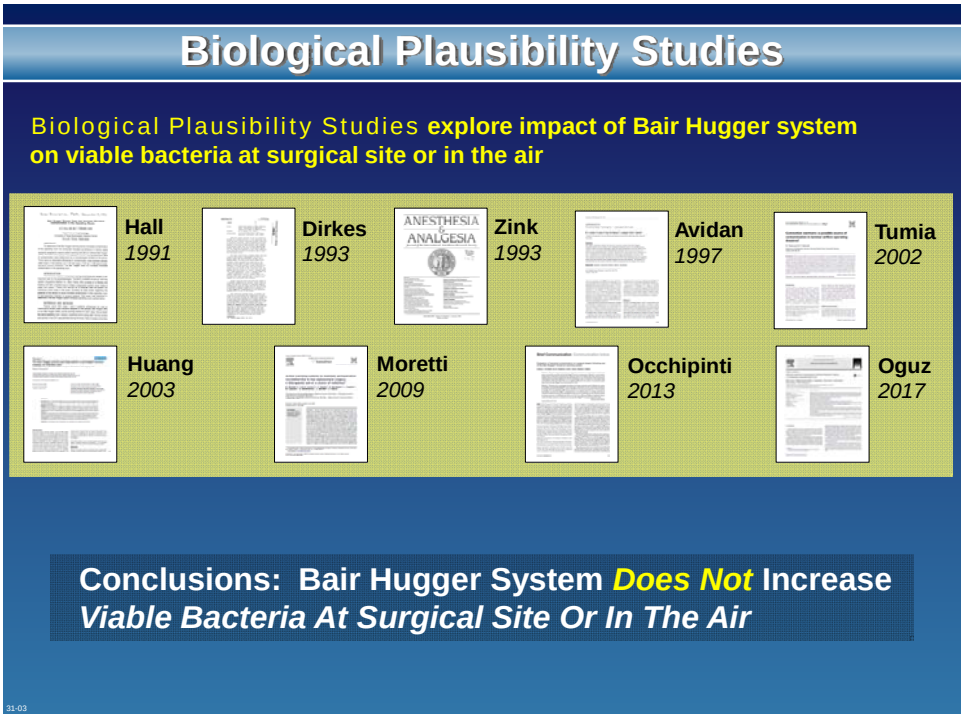
Kurz
1996

Melling
2001

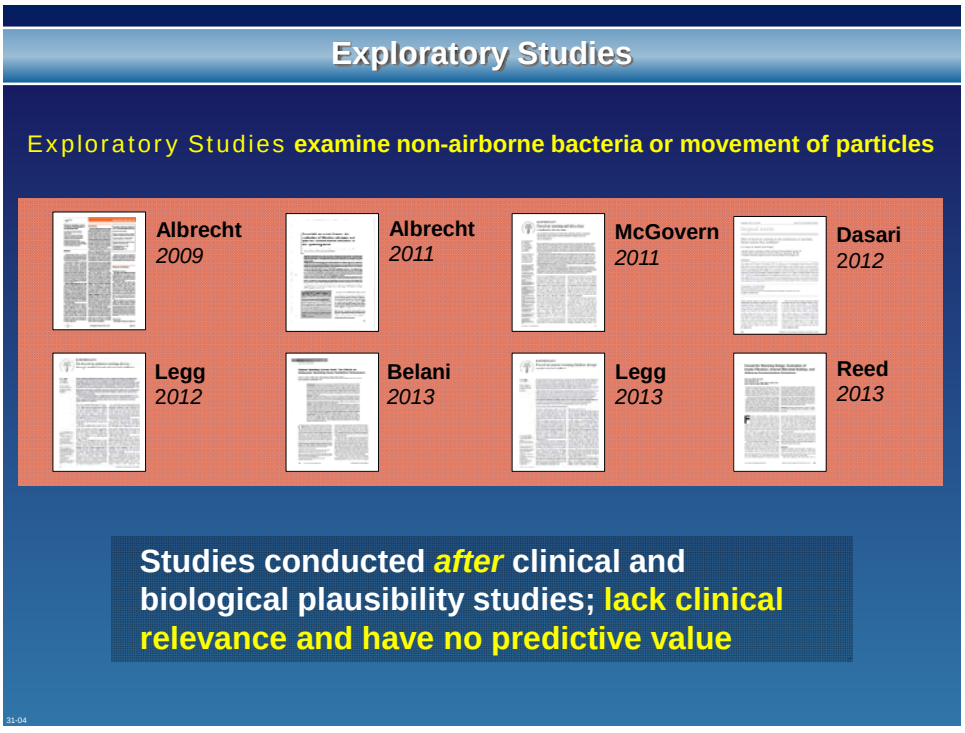
Conclusions: Bair Hugger System *Reduces* Surgical Site Infections

31-02

2c. Biological Plausibility Studies



2d. Exploratory Studies



IV. The Microbiome

Introduction: Infection is a multifactorial event with several contributing aspects to the risk. For any given mode of transmission (direct contact, fecal-oral, airborne, blood borne, large droplet and others), the infectious risk is influenced by the following:

- Organism exposure dose and inherent virulence
- Environmental risk factors
- Host factors

In surgical site infections, host factors are very important. These include the participants' own comorbidity risk factors, genetics, immune status, and the microbiome of the patient. Below I introduce the concept of the host microbiome as part of host defense against infections.

a) Role of the Microbiome

The term microbiota is commonly used to describe the community of microorganisms (bacteria, yeasts, viruses) that colonize our skin, nasal passages, throat, vagina and gastrointestinal tract. The term *microbiome* is used to define the total aggregate of microbial genes located at a specific part of a person's body. I will use the term microbiome for both. Since many species of the microbiome cannot be cultured using standard methods, investigators have used new techniques to identify microbial genes to study the microbiome. A healthy microbiome assists people in warding off the very offensive bacteria e.g. strep or staph that can cause serious infections. People and various microorganisms colonizing the human body live in a "peaceful coexistence" relationship if we remain healthy. If the numbers of some bacteria become very large, if the bacterial composition of the microbiome is altered, or if the person's immune system fails, however, infection can occur.

Not surprisingly, antibiotics can sometimes kill off some of the "good" bacteria and allow a harmful one to dominate and cause infection. An example of the latter is the appearance of *Clostridium difficile* colitis, a serious and sometimes life-threatening infection of the colon after antibiotic use. The antibiotics kill off the "good" flora of the intestine, cause major alteration in bacterial composition, and select for the overgrowth of the *Clostridium difficile*. What is striking is the almost complete reversal of the infection in days after restoration of normal flora. (See S. Khanna et al, A Novel Microbiome Therapeutic Increases Gut Microbial Diversity and Prevents Recurrent Clostridium difficile Infection, *J. Infect Dis* 2016; 214: 173-81; Vehreschildet al., Fecal Microbiota Transfer 2.0, *J Infect Dis 2016;* 214: 169-70).

b) Numbers of bacteria of the microbiome

A perspective on the importance of the microbiome relates to numbers: on our body we have 10^{13} human cells (a 1 followed by 13 zeros). However, on our skin and mucous membranes we have 10^{14} microorganisms – thus 10 times as many microbes as human cells! When one examines the aggregate of microbial genes, they outnumber human genes by a factor of 1000 (EA Grice, The skin microbiome: potential for novel diagnostic and the therapeutic approaches to cutaneous disease, *Semin Cutan Med Surg 2014*; 33: 98-103). It is now recognized that the community of microbes and their genes can influence the outcome of the interaction of people and microbes. The same genus and species can cause serious infections in some patients and become "neutral," colonizing bacteria in others.

On the skin, each of the bacteria, yeast, and virus family members of the microbiome has a preferred location on the body, depending on local moisture or distribution of sebaceous glands or hair follicles, etc. Thus, certain organisms dominate some sites on the body and other organisms on other parts. If we injure our skin, an infection may result and is often due to the organisms living nearby on that part of the skin.

In people, maintaining a protective community of usual microbes on the body is important for health.

c) The role of the microbiome and surgical site infections

Without the protection of the skin barrier nearby, organisms that are part of the skin microbiome can invade the deeper layers of the skin and soft tissue below. In surgery, the integrity of the skin is disturbed by the incision, posing a risk of infection: organisms living in harmony in the nose, throat or skin near the incision can find their way to the incision site and cause a surgical site infection (SSI).

A cross-section of the skin (figure 3) shows the top layers of the epidermis and dermis, below which lies the subcutaneous fat tissue and then the muscle and bone tissues. Piercing the dermis are the tubules from the sweat glands and hair follicles of the sebaceous glands, located in the subcutaneous tissue. [Figure 4].

The sweat glands help regulate temperature, and the sebaceous glands provide sebum which lubricates the top layers of skin and provides a water proof surface.

Figure 3

Importantly, bacteria of the microbiome reside not only on the skin surface but also on the hair follicles and in both the sweat glands and sebaceous glands (figure 4).

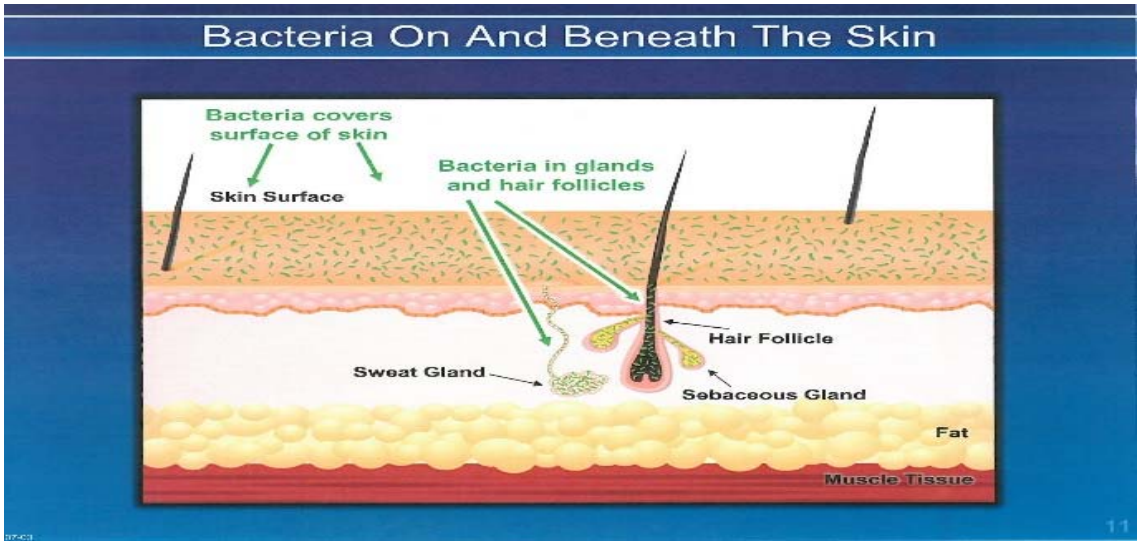


Figure 4

At the time of surgery the skin near the incision is prepped with an antiseptic designed to reduce the numbers of bacteria there. However, no current skin prep will kill all the bacteria on the surface nor the organisms below the surface in the sweat glands or sebaceous glands.

One can now see that if we could control the microbiome, we might prevent SSIs. Specifically for clean surgery, if we can control the microbiome of the skin and nasal passages, we will reduce the rate of SSI. Conversely, if we fail to control the microbiome, a surgical patient will develop a surgical site infection. Prior to surgery we physicians attempt to control the patient's microbiome by suggesting chlorhexidine showers to reduce the burden of staphylococcus and other bacterial counts on the skin; topical nasal antibacterial creams to "decolonize" the nose of *Staphylococcus aureus*; and best skin antiseptic preps just before the incision. To reduce the burden of infectious organisms in general, intravenous antibiotics are administered preoperatively to achieve a high blood and subcutaneous tissue concentration at the time of the incision.

Some patients are at higher risk than others for getting a surgical site infection by virtue of their having some underlying conditions such as diabetes mellitus, older age, obesity and other "comorbidities." It is thought that these conditions in some way alter the body's immune system or change the composition or nature of the microbiome.

Changes in the microbiome of the intestine have been noted in the following conditions: Obesity, diabetes mellitus, celiac disease, and others.

I am unaware of definitive studies to examine the skin microbiome in all of these conditions. However, an early study of *S. aureus* nasal carriage in children and in adults showed higher carrier rates in diabetics: See Smith JA et al, Basal Carriage of Staphylococcus aureus in Diabetes Mellitus, Lancet 1966 pp 776-7.

Children (157/531 were diabetic)

S. aureus Carriage:

Diabetics 76%

Non-Diabetics 44%

Adults (324/578 were diabetic)

S. aureus Carriage:

Insulin Dependent Diabetics 53%

Non-Insulin Dependent Diabetics – 35%

Non-Diabetic 34%

In 2008, Gorwitz RJ et al reported on the changes in the prevalence of nasal colonization with S*taphylococcus aureus* in the United States, 2001 – 2004. In the NHANES survey they found that **colonization with MRSA was independently associated** with healthcare exposure in males, with U.S. born, age >16, **diabetes**, and poverty in females. (Gorwitz et al., Changes in the Prevalence of Nasal Colonization with Staphylococcus aureus in the United States, 2001-2004, J Infect Dis 2008; 197: 1226-34).

A 2006 study of *S. aureus* carriage in diabetics and non-diabetics in Japan showed that independent risk factors for carriage were insulin use (OR 3.32) and antibiotic usage within the prior six months (OR 5.750). (See, Tamer et al., Staphylococcus aureus in Nasal Carriage and Associated Factors in Type 2 Diabetic Patients, Jpn. J. Infect Dis. 2006; 59: 10-14).

In a study of 137 cases of community – associated MRSA (CA MRSA) cellulitis, the independent risk factors for MRSA vs other causes of cellulitis - included obesity (AOR 2.33 – CI_{95} and the presence of abscesses (AOR 2.72 - CI_{95} 1.27 – 5.83). (See Khawacharoenporn, et al., Risk Factors for Community – associated Methicillin-resistant Staphylococcus Aureus Cellulitis – and the Value of Recognition, Hawai Med J, 2010; 69: 232-6)

In a study of obesity and *Staphylococcus aureus* nasal colonization among 2169 women and 1709 men in a general population, Olsen and colleagues found that in women**, each 2.5 kg/M^2 increase in BMI was associated with a 7% higher odds of *S. aureus* nasal colonization (p=0.01).** BMI was not associated with *S. aureus* nasal colonization in men, but high waist circumference was linked in men to *S. aureus* nasal carriage.

See Olsen K et al, Obesity and Staphylococcus *aureus* nasal colonization among women and men in a general population. P105ONE 2013: 8(5); e 63716. doi: 10. 1371/journal.pone.0063716.

Herwaldt LA et al described preoperative risk factors for nasal carriage of *Staphylococcus aureus*. Of 4030 patients, 891 (22%) carried *S. aureus.* **Independent risk factors for *S. aureus* nasal carriage included obesity (OR 1.29 with CI_{95} 1.11-1.50);** male gender (OR 1.29 with CI_{95}) 1.11 – 1.51); and a history of cerebrovascular accident (OR 1.53 with CI_{95} 1.03 – 2.25). (Herwaldt et al, Preoperative Risk Factors for Nasal Carriage of Staphylococcus aureus, Infect Control Hosp Epidemiol 2004; 2: 481-4.)

With respect to the microbiome one can say that certain conditions alter the composition such that diabetes and obesity increase nasal carriage of *S. aureus*. Nasal carriage of *S. aureus* is inked to increased risk of *S. aureus* SSI. Both diabetes mellitis and obesity are linked to increased risk of SSI, and some portion of that risk can be accounted for by the altered microbiome of the nasal passages.

Recently two microbiologists suggested that we abandon the term "pathogen' and instead focus on the reaction that occurs when a microbe interacts with a person. That interaction, described by Casadevall and Pirofski, yields one of three possibilities: infection (damage occurs); colonization (indifference) or commensal (benefit). These authors now incorporate the microbiome into the model, implying that variations in a person's microbiome influence the host response to a microbial challenge. Thus, a person and her microbiome are inseparable. (Casadevall and Pirofski, Ditch the term pathogen: disease is as much about the host as it is the infectious agent-the focus on microbes is hindering research into treatment, Nature 2014; 516:165-7.)

Interim Summary

We can think of the microbiome as part of the body's immune defense system. So in simple terms, if in any way we alter the microbiome defense system, the risk of infection rises. Both the density of the organisms and the composition are important factors.

When a patient requires surgery, it is important to assess that individual's risk for infection: What are the underlying illnesses that might alter the microbiome and increase risk? Has the patient been on antibiotics in the past 6 months that might have altered the composition of the microbiome? Are there several underlying problems such as obesity or diabetes that might combine to alter the microbiome and add risk for a surgical site infection? Afterwards we might ask, if a patient acquires a SSI, what is the likely origin of the offending organism causing the infection, and could it have become a preoperative member of the microbiome? Were all opportunities to reduce the risk of a SSI met with a good response?

d) Skin microbiome as the key source for SSIs after clean surgery

In 2010, Rabih Darouiche and colleagues reported a study comparing two alternative skin preps for reducing SSIs. In a study at 6 hospitals, 849 patients were randomized to receive the standard povidone iodine antisepsis vs chlorhexidine – alcohol skin prep. Within 30 days of surgery, infection occurred in 16.1% assigned to the standard povidone-iodine vs 9.5% assigned to the chlorhexidine – alcohol arm. **The use of a chlorhexidine-alcohol skin prep is linked to a 40% *incremental* reduction of all SSIs resulting from reducing the microbiome of the skin at the area of the incision. (Dariouche, et al., Clorhexidine-Alcohol versus Povidone-Iodine for Surgical Site Antisepsis, N Eng J Med 2010; 362: 18-26.)**

In another study, among 1147 patients undergoing a caesarian delivery those assigned randomly to chlorhexidine – alcohol prep had a relative risk of a SSI of 0.55 (CI_{95} .30-.90), compared to these whose iodine-alcohol. **Thus, reducing the microbiome with a better prep reduced SSI by 45%.** This study again illustrates the critical role of the microbiome. (*New Engl J Med* 2010; 362:18-26. M.G. Tuuli et al., A Randomized trial comparing skin antiseptic agents at Cesarean delivery, N. Eng *J Med 2016*; 1-9)

The 40% reduction in surgical site infections after better controlling the microbiome of the skin with topical chlorhexidine alcohol is an incremental improvement – above that expected with povidone-iodine. Although there are no clinical trials of povidone – iodine vs placebo control in surgical patients, some insight into the value of povidone iodine can be gleaned from the study by A. Gravett et al. That team performed a prospective, randomized study of 500 consecutive patients entering the emergency room with traumatic lacerations requiring sutures. Half of the group had a wound irrigation with normal saline without scrubbing, and half had a 60 second wound irrigation and scrubbing with 1% povidone – iodine (Gravett et al., A trial of povidone-iodine in the prevention of infection in sutured lacerations, Ann Emerg Med 1987; 16: 167-71).

Of the 201 povidone – iodine wounds followed up, 11 became infected (5.4%) (2 became purulent). Of the 194 control wounds followed, 30 became infected (15.5%) $p< 0.01$(12 were purulent). **Thus, in that study ~ two-thirds of possible infections were eliminated with povidone – iodine and one-third remained.**

If similar data would apply to general surgery patients ie if povidone iodine was already preventing two-thirds of infections, then removing an incremental 40% on the remaining one-third with a switch to a chlorhexidine – alcohol prep would be an absolute removal of an additional 13% (40% times 1/3 residual). The absolute remaining proportion of wounds still not controlled with chlorhexidine – alcohol would be one-third (33%) minus 13% or 20%. This rough estimate based on clinical trials suggests that 80% of potential SSIs can be currently eliminated with control of the microbiota of the skin. Even if povidone-iodine reduced total infections by only one-third, the 40% reduction of the remaining two-thirds (27%) plus the 33% already controlled by povidone iodine would imply a 60% control currently with skin prep alone. (Figure 5).

(See Gravett et al. A trial of povidone – iodine in the prevention of infections in sutured lacerations. Ann Emerg Med 1987; 16: 167 – 71.)

Modeling Residual SSI Source with Increasing Efficacy of Skin Preps

If Iodine Reduces 2/3 SSI

1/3 (33%) SSI Residual

If Iodine Reduces 1/3 SSI

2/3 (67%) SSI Residual

Figure 5

Further reduction of residual by 40% with chlorhexidine – alcohol

33% - 13%

67% - 27 %

20% residual

80% SSI eliminated

20% Residual

60% SSI Eliminated

40% Residual

40% residual

e) Mapping the Microbiota of the Skin – A Marker organism, *Propionibacterium acnes*

In recent years it has become possible to begin to map the microbiome of the skin by looking at the genes of the bacterial microbiome at specific locations, a much more sensitive approach than cultures of organisms. Among the findings are that *S. aureus* is common to all areas of the skin but especially so in the under arm, groin, the webs of toes – areas of high humidity. Additionally, the upper back and upper chest is disproportionately colonized with

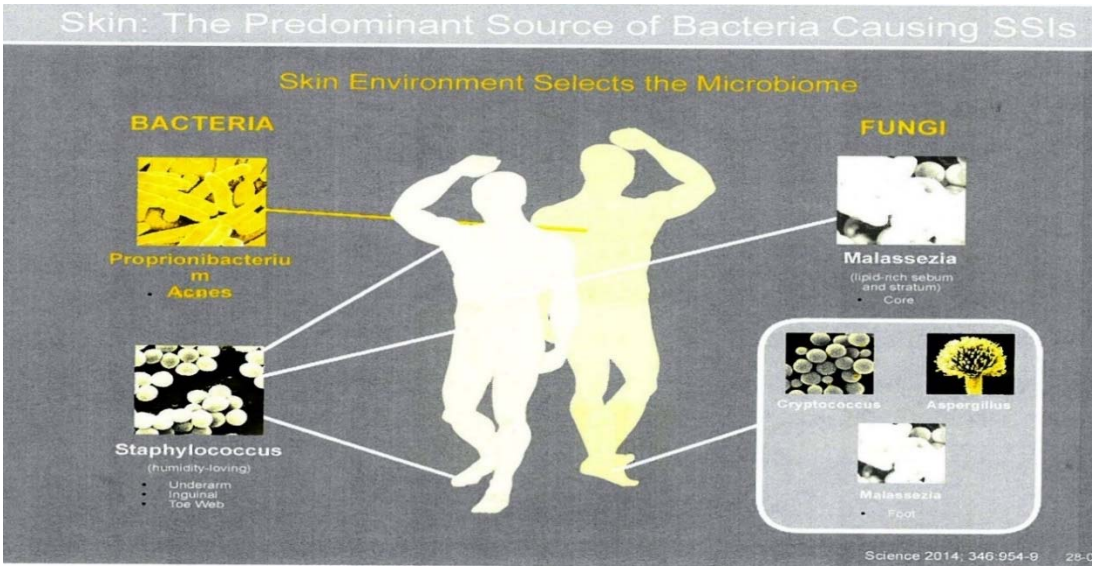


Figure 6

Propionibacterium acnes, an anaerobic, rod – shaped organism that prefers the environment of high levels of sebaceous glands. This species uses the sebum produced by sebaceous glands to grow and to metabolize to free fatty acids that help bind the organism to the upper back and upper chest. (Figure 6). If the local microbiome is the source of SSIs, one might expect that infection near the shoulder would show this marker organism more often than infections after knee or hip surgery that involve incisions over body surfaces not prevalent with sebaceous glands and *P. acnes.*

In that respect, it is of interest is to examine the bacterial causes of prosthetic joint infections (Figure 7). Whereas *S. aureus* and coagulase – negative staphylococci account for 43-83% of infections after joint implants, 24% of infections of shoulder joint prostheses are caused by *P. acnes*, the organism living near

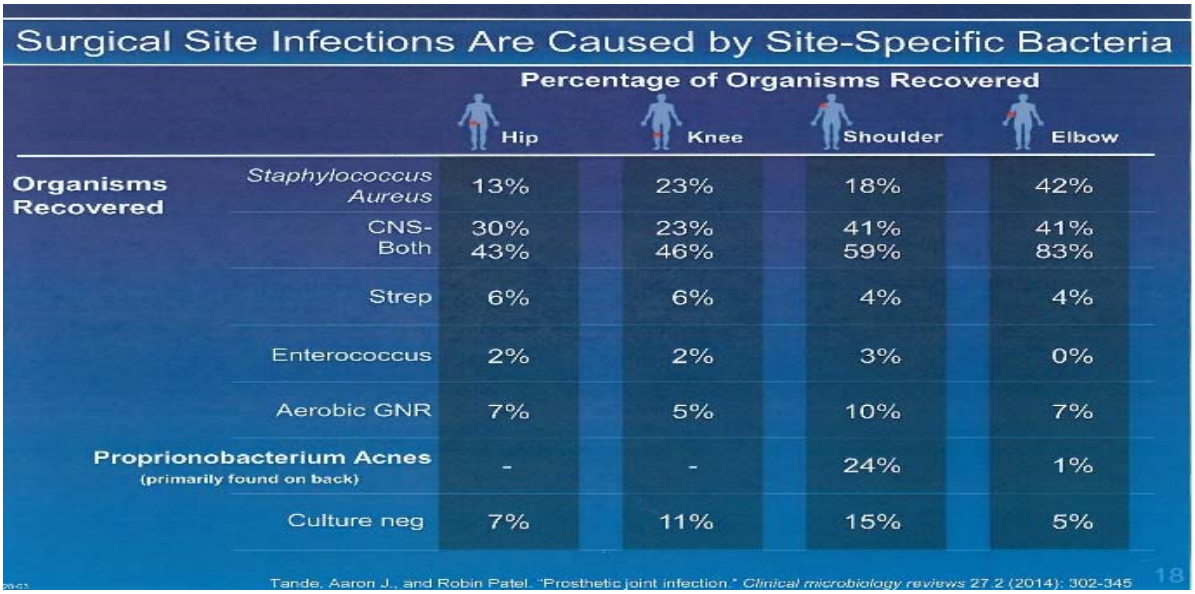


Figure 7

the incision site for that operation. It is commonly found in shoulder prosthetic joint infections. (See Tande A and Patel R., Prosthetic Joint Infection, *Clin Micro Rev* 2014; 27: 302-45). This is a useful organism to study SSIs, since it is a marker organism, one not ubiquitous as coagulase negative staphylococci.

Corroborating findings include the fact that up to 51% - 56% of infections after rotator cuff surgery of the shoulder are caused by *P. acnes*. *P. acnes* is not found commonly after joint surgery of hips or knees or elbows. (P.Y. Levy et al., Propionibacterium acnes Postoperative Shoulder Arthritis: An Emerging Clinical Entity, Clin. Infect Dis 2008; 46: 1884-6; G.S. Athwal et al., Deep infection after rotator cuff repair, J Shoulder Elbow Surg 2007; http:// dx.doi.org/10.1016/S. JSE 2006.05013).

In addition to the link of the microbiome near the shoulder and subsequent infections with *P. acnes* are also supportive microbiological data on similar patients with shoulder surgery:

- P.M. Sethi and colleagues examined the frequency of *P. acnes* found in 57 patients undergoing primary shoulder arthroscopy. Most patients (58%) were undergoing rotator cuff repair. Positive skin cultures for *P. acnes* were found in 8.8% of patients before the incision and after the skin prep but as high as 31.9% at closure. 56% of patients had at least 1 positive culture, and 22.8% had $\geq$ 3 positive cultures.

(Sethi et al., Presence of Propionibacterium acnes in arthroscopy: results of aspiration and tissue cultures, J Shoulder Elbow Surg 2015 796-803, http://dx doi.org/10.1016/j.jse.2014.09.042)

In the discussion the authors noted that Matsen et al found *P. acnes* in 76% of non-prepped skin and an intraoperative 55% rate of positive cultures for a dermal layer in another patient group. Similar to the data of Sethi et al, Saltzman et al found only a 7% rate of *P acnes* after chlorhexidine – alcohol skin prep. (See F.A. Matsen et al, Origin of Propionibacterium in Surgical Wounds and Evidence Based-Approach for Culturing Propionibacterium from Surgical Sites, J Bone Joint Surg Am 2013; 95 (23): @ 1811-7. http:// dx.doi. org/10.2106/JBJS. L. 01733)*M.D. Saltzman, et al, Efficacy of Surgical Preparation Solutions in Shoulder Surgery, J Bone Joint Surg Am 2009; 91: 1949-53. http://dx.doi.org/10.2106/JBJS.H. 00768.*

Thus, the organism is nearby, accounts for a significant proportion of infections seen, in both rotator cuff shoulder repair and infections after prosthetic shoulder replacement, and is apparently not well controlled with existing antiseptic preps. It is already present at the surgical site before the incision.

- Sethi's group followed up with a study of the efficacy of topical benzoyl peroxide on the reduction of *P. acnes* culture during shoulder surgery.
  (J.R. Sabetta et al., J Shoulder Elbow Surg. 2015, 995-1004; http://dx.doi. Org/10.1016/J.JSE. 2015. 04.003)

The authors recognized that *P. acnes* resides in the sebaceous glands, that chlorhexidine – alcohol prep was inadequate for eliminating the organism at the time of surgery, and that benzoyl peroxide (BPO) commonly used to treat acne, penetrates the pilosebaceous duct. They hypothesized that BPO would incrementally reduce the burden of *P. acnes* in addition to the skin prep with chlorhexidine-alcohol. 5% BPO was administered topically twice a day preoperatively and on the morning of surgery – 5 doses total.

50 patients were studied, and most (68%) were undergoing rotator off repair. Before the skin prep, 16% of the BP0 surgical site had *P. acnes* vs 32% on the skin of the deltoid on the untreated arm p=0.0001. The axilla was positive in 8% of BPO treated arms vs 28% of the untreated arms (.p=0.013).

After skin prep, with 3 applications of 2% chlorhexidine gluconate, 6.25% of samples grew *P. acnes* – a non-significant difference from control air swabs at 4%. At the end of surgery, 10% of skin cultures were positive, also not significant from air swab cultures.

The BPO application reduced pre-prep cultures by ~ 50% vs the control arm. **After adding the chlorhexidine alcohol prep, there was a further reduction of positive cultures for *P. acnes* from 16% on the deltoid to 6%, and from 32% in the axilla to 6% (See Table below):**

Rate of Positive *P. acnes* Cultures by Specimen

Control Air Swab 4% End of procedure : Axilla surgical side – 10% Skin anterior deltoid surg side – 10%	Skin anterior deltoid/Axilla Before preps: BPO side deltoid – 16% BPO side axilla – 8% No BPO side deltoid – 32% No BPO side axilla – 28% ↓ After skin prep ↓------ Ant deltoid surg side – 6% Axilla surg side – 6% Joint fluid – 4 % Tissue 1, 2,3-6%, 2%, 6%

The study confirms the dermis as the primary source of *P acnes;* BPO – a drug that penetrates the pilo-sebacious gland microbiome - reduced the risk of having a positive culture for *P acnes*, above a baseline and also above the rate seen after a skin prep. This drug has not been tested to measure its efficacy in reducing SSIs.

Currently, best estimates are that with improved skin preps the microbiome is better controlled and SSI rates have been reduced by 60-80%. With the marker organism, *P acnes*, proof of concept of the need to control the microbiome prior to shoulder surgery was shown with BPO, a drug that penetrates the pilo-sebacecus gland, affecting the microbiota.

- The skin adjacent to the spine is also a site for *P. acnes* residence. Among 489 patients operated on for correction of scoliosis studied by Richards and Emara, 23 developed delayed infection. *P. acnes* was positive in 12 (53%) of the 23 patients in the specimens obtained at the time of instrumentation removal (Richards, et al., Delayed Infections After Posterior TSRH Spinal Instrumentation for Idiopathic Scoliosis: Revisited, Spine 2001; 26: 1990-5). In another study, Sampedro and colleagues cultured the spinal implants of 22 patients with SSI and detected *P*

acnes in 9 (41%) of the 22 patients. (Sampedro, et al., A Biofilm Approach to Detect Bacteria on Removed Spinal Implants, Spine 2010; 35: 1218-24). In a third study, Shiono and colleagues sent specimens for culture during spine correction surgery for scoliosis (N=80): 1) Swabs of the skin after povidone – iodine prep but before draping; 2) laminae bone immediately after exposure; 3) laminae bone immediately after screw placement; 4) laminae bone immediately before wound closure; 5) bone fragment immediately after exposure and kept covered; and 6) a bone fragment immediately after exposure but kept uncovered.

No SSIs occurred. Positive cultures for bacteria were found in 1) 31%; 2) 25%; 3) 31%; 4) 33%; 5) (7.5%) and 6) 9%). *P. acnes* were recovered in 15 and *P. species* in another 9. Aerobic Gram positive cocci were found in 3 and other bacteria in 6 specimens (Shiono, et al, Sterility of Posterior Elements of the Spine in Posterior Correction Surgery, *Spine* 2012; 6: 523-6). These are further data supporting the concept that local flora at the site of the incision harbor the bacterial that cause a large proportion of SSIs. The study by Shiono et al shows also that organisms are present soon after skin prep and soon after incision. Brian Walcott and colleagues in a review of infections following operations on the central nervous systems states that "..bacteria penetrate the wound at the time of the initial surgical exposure. It is likely that most wound infections are the result of direct contamination with the local microbiome…" The subtitle of his article is "deconstructing the myth of the sterile field" (Walcott, et al., Infection following operations on the central nervous system; deconstructing the myth of the sterile field, *Neurosurg. Focus* 2012; 33: 1-9, DOI: 10.3171/2012.8.FOCUS12245). The implication is that surgeons do their best to minimize the number of bacteria at the incision site, but it is never sterile but as clean as possible, given the microbiome and human activity in disturbing the microbiome.

Corroborating support that the airborne route of infection is not common in surgery and that the patient's microbiome is the source comes from observational data of Tammelin and colleagues. They prospectively studied a cohort of 65 adults undergoing elective coronary artery bypass grafting – with or without concomitant value replacement. They focused on the source and route of transmission of methicillin – resistant *Staphylococcus epidermidis* (MRSE) in the surgical wound (Tammelin, et al, Source and route of methicillin-resistant Staphylococcus epidermis transmitted to the surgical wound during cardio-thoracic surgery. Possibility of preventing wound contamination by use of special scrub suits, *J Hosp Infect* 2001; 47: 266-76).

Pre-incision cultures of the sternum and legs (vein donor site), air cultures in the operating room, OR staff members' cultures of hands after the initial scrub, and wound cultures just before closing were examined. Patients with MRSE on sternal skin had a higher rate of MRSE in the wound than those with no MRSE on the sternal skin (RR = 2.429 CI_{95} 1.43-4.10). Recovery of MRSE in the air during operation or on the hands of the scrubbed team was not linked to finding MRSE in the wound. The significance of sternal skin as the source of MRSE wound contamination was supported by fingerprinting the organisms (pulse field gel electrophoresis): 3 of 4 traceable isolates originated from the sternal skin at the incision site. In the same study patients were divided into those whose surgical team wore conventional scrub suits with a fabric air permeability of 121.L/min vs those with a cotton and polyester weave mid an air permeability of only 2.5 L/min. No mention of randomization was made. The authors note that the reduction of total air counts of bacteria by use of the tightly woven scrub suits did not reduce the air counts of MRSE or wound contamination with MRSE.

f) *S. aureus* Carriage and Risk of a SSI

One of the most feared organisms in prosthetic wound infections, and very common is *S. aureus*. A key question is where did the *S. aureus* originate? Data from various studies indicate that the majority come from the patients themselves. Furthermore, controlling the microbiome of the nares with topical antibiotics is linked to a significant reduction in *S. aureus* SSIs.

In the pre- Bair Hugger era (1959 – 1969), it was shown that 33 to 100% of surgical patients in 8 different studies had *S. aureus* SSIs that matched the strains carried in their nares. (See review by Wenzel and Perl J *Hosp Infect* 1995; 31:13-24. – The following Table is from that review).

S. aureus surgical site infections and the proportion of endogenous sources

Rates of postoperative wound infection in nasal carriers and non-carriers of *Staphylococcus aureus*

Rates of wound infection

First author	Year of report	No. infected/ No. colonized	No infected/ No. not colonized	% Endogenous*
White	1964	20/106 (19%)	28/345 (8%)	66
Williams	1959	20/276 (7%)	7/342 (2%)	55
Public Health Laboratory	1960	73/821 (9%)	158/2235 (7%)	33
McNeill	1961	12/74 (16%)	11/113(10%)	42
Henderson	1961	22/264 (8%)	18/569 (3%)	30
Bassett	1963	24/442 (5%)	6/78 (8%)	58
Calia	1969	19/96 (17%)	16/173 (9%)	100

* By phage-typing-showing same strains in preoperative nasal culture as identified in postoperative wound infections.
In none of the studies was the pathway to infection studied among carriers.
From a review by Wenzel RP and Perl TM, The significance of nasal carriage of staphylococcus aureus and the incidence of post-operative wound infections.
J Hosp infect 1995; 31:13-24.

The data show the rates of *S. aureus* SSIs among surgical patients who were *S. aureus* carriers were 2 to 3 times greater among carriers than non-carriers. *The Bair Hugger had been in use for only 25 years in 2012; thus, none of these studies above were performed in the era of the

Bair Hugger. Thus, the carriage of *S. aureus* has been a recognized risk factor for *S. aureus* SSIs independent of forced air warmers.

Data from the review, shown in the table, illustrate the strong association of *S. aureus* SSIs and prior carriage of the same organism by patients undergoing surgery. The median data among studies showed that 55% of SSIs were endogenous strains carried pre-operatively (Williams). It is unclear how the patients acquired the infection, but they occurred without any warming device in use.

These data – well before the advent of the Bair Hugger – were confirmed in a 1963 report by J Burke from Harvard. In their quest to identify the sources of staphylococci contaminating the surgical wound during operation, they found that in 50% of operations studied (N=50), **"Strains of staphylococci found in the patients' nose, throat or skin in the region of the proposed surgical wound were also identified in the wound just prior to closing."** (John F. Burke, Identification of the Sources of Staphylococci Contaminating the Surgical Wound During Operation, Ann Surg 1963; 158:898-904).

In a study of the safety and efficacy of intranasal mupirocin for the elimination of *S. aureus* carriage, Reagan and colleagues showed the following (Reagan, et al. Elimination of coincident *Staphylococcus aureus* nasal and hand carriage with intranasal application of mupirocin calcium ointment, Ann Intern Med 1991; 15:101-6).

Among nasal carriers of *S. aureus*, 30-50% had the same organism on their hands pre-treatment, and elimination of nasal carriage was significantly linked to a reduced hand carriage after therapy: 2.9% in the treated group vs 57.6% in the controls. This 53% difference was significant, after adjustment for the baseline frequency of hand carriage.

This study shows that nasal carriage is a marker for *S. aureus* carriage elsewhere on the body, and elimination of nasal carriage is linked to elimination of non-nasal carriage.

L.A. Mermel and colleagues examined known carriers of MRSA (N=60) and examined nasal and extranasal colonization. Samples showed positive cultures of $\geq$ 1 site in 53 of the 60. Sensitivity for a positive culture was 91% for nares, 63% for groin, 47% for perineum and 32% for the axilla. A relationship was found for $\log_{10}$ counts in the nares and greater number of body sites colonized with MRSA. A correlation between diabetes and $\log_{10}$ counts in the perineum was shown. (L. A. Mermel et al. Methicillin – Resistant *Staphylococcus aureus* colonization at different body sites: A prospective quantitative analysis. J Clin Micro 2011; 49:1119-21).

Since nasal carriage predicts carriage of *S. aureus* in the groin and perineum, it is reasonable to postulate that failure to control the carriage in the nose leads to failure to control the microbiome of the groin and perineum.

A number of more recent studies show similar results to those in the pre-Bair Hugger era. In a follow up randomized clinical trial among surgical patients, in the subset with nasal carriage of

S. aureus, 4 percent of those who received preoperative nasal mupirocin had nosocomial *S. aureus* infections vs 7.7 percent of those who had received placebo (OR 0.49 [CI_{95} .25 to .92]. (Perl TM et al., Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. *N Engl J Med* 2002; 346: 1871-7)**.**

In a 2010 report of a clinical trial in preoperative nasal carriers of *S. aureus* using either nasal mupirocin ointment plus chlorhexidine soap vs placebo, the rate of *S. aureus* infection was 3.4% vs 7.7 %, respectively. The relative risk was 0.42 [CI_{95}. 23 - .75]. **Thus, almost 60% of *S. aureus* SSIs were prevented with current control of the microbiota of the nares and skin.** The effect was more pronounced for deep surgical infections with a risk ratio of 0.21 [CI_{95}. 07 to .62]. (Bode et al., Preventing surgical-site infections in nasal carrier of *Staphylococcus aureus, N Engl J Med* 2010; 362: 9 – 17).

In a cohort of 272 orthopedic patients in which risk factors for SSIs were examined, the only independent predictor of SSI due to *S. aureus* was high – level nasal carriage of *S. aureus* (P=0.002). (Kalmeijer et al., Nasal carriage of staphylococcus aureus is a major risk factor for surgical-site infections in orthopedic surgery, *Infect Control and Hosp Epidemiology* 2000; 21:319-23).

In a double-blind, randomized, placebo – controlled study among orthopedic surgical patients (N=614), eradication of nasal carriage of *Staphylococcus aureus* was 83.5% among those who were treated preoperatively with nasal mupirocin vs 27.8% in placebo recipients. All patients had prosthetic implants for hip, knee or back surgery. <u>The rate of endogenous infections was 5 times lower in the mupirocin group (0.3%) vs the placebo group (1.7%).</u> The total *S. aureus* SSI rate was 1.6% for the mupirocin group vs 2.7% for the placebo group. RR.59 (.20 – 1.79) – 63% reduction but not statistically significant. (Kalmeijer, et al., Surgical Site Infections in Orthopedic Surgery: The Effect of Mupirocin Nasal Ointment in a Double-Blind, Randomized, Placebo-Controlled Study, *Clin Infect Dis* 2002; 35(4): 353-8).

The above data have prompted one team of orthopedic surgeons recently to state that "for patients undergoing surgery requiring a prosthetic implant, nasal colonization with *S. aureus* is the most important independent risk factor for the development of an SSI." Goyal et al., Methicillin – resistant *Staphylococuss aureus* (MRSA), Colonization and pre-operative screening. (*Bone Joint J* 2013; 95-13: 4-9).

In a cross-sectional analysis of *S. aureus* nasal colonization in 284 orthopedic patients preoperatively, Price et al found that 30% carried *S. aureus* of whom 6% were MRSA; by 2005, 4% of such patients were MRSA carriers preoperatively. Of 282 evaluable patients, 9 (3.2%) developed infection. Five of 9 occurred in the arthroplasty group (N=94), four had *S. aureus* – 3 MSSA and 1 MRSA. (C.S. Price et al, Staphylococcus aureus Nasal Colonization in Preoperative Orthopaedic Outpatients, *Clin Orthop Relat* Res 2008; 466:2842-7).

The risk of infection following colonization with MRSA was found to be 4-fold greater than with MSSA colonization – in a review of 10 observational studies of 1170 patients. (Safdar et al, The

Risk of Infection after Nasal Colonization with Staphylococcus Aureus *Am J Med* 2008; 121; 310-15).

The risk of subsequent prosthetic joint seeding after a *S. aureus* bacteremia is also very high: David Murdoch and colleagues prospectively examined 57 patients with prosthetic joints who developed *S. aureus* bloodstream infection: 15/44 or 34% developed a prosthetic joint infection as a result. This contrasted with 1/15 or 7% with other not joint orthopedic devices. (Murdoch et al., Infection of Orthopedic Prostheses after Staphyloccus aureus Bacteremia, *Clin Infect Dis* 2001; 32(4):647-49).

Note: For general surgery and surely for orthopedic implant surgery, it is critical to eliminate *S. aureus* SSI and controlling the microbiome of the nares is key to minimizing *S. aureus* SSIs.

As shown above, in the last 15 years it has been shown that intraoperative warming decreased SSIs by ~ 65 – 75% from the baseline. Because warming is linked to increased subcutaneous tissue oxygenation, the data are consistent with the idea that the microbiome of the skin (numbers or composition or function) is better controlled with perioperative warming.

The data on nasal carriage alone show that control of the microbiota of the nares can incrementally reduce *S. aureus* SSIs by ~60% - 84%. This organism alone comprises 13% - 42% of prosthetic joint infections (Figure 5).

In the Bode et al study in which *S. aureus* SSIs were reduced by 60% with mupirocin and chlorhexidine skin washes, that reduction accounted for an absolute reduction of SSI of 7.5%.

If control of the microbiome of the skin currently has a residual SSI proportion of 20 – 40% (figure 5), addition of nasal mupirocin preoperatively would reduce the residual by almost 10% more. Thus, the updated residual proportion of SSI might be ~ 10% to 30% in 2017 with current control of the microbiome of the skin and nares. **The point is that the vast majority of SSIs are currently recognized by available techniques to be endogenous – from the patients themselves, and studies show that SSIs can increasingly be controlled with better control of patients' microbiome.**

g) Newer Data on the Microbiome

In recent years it has been shown some patients (~20%) carry MRSA in the throat only – not in the nares. Since nasal carriage of *S. aureus* including MRSA is a risk for subsequent SSIs and since no routine perioperative protocol examines for or tries to eliminate throat carriage of *S. aureus* it is reasonable to propose that such carriage could be a risk for SSIs. (See Dalziel, et al., Nasal and Pharyngeal Carriage of Methicillin-resistant Staphylococcus aureus (MRSA) in Undergraduate Nursing Students, www.Asmoline.Education.com/php/ASM 2014; and Mertz et al, Throat Swabs Are Necessary to Reliably Detect Carriers of Staphylococcus aureus, *Clin Infect Dis* 2007 43:475-77; and Mertz, et al, Exclusive Staphylococcus aureus Throat Carriage, *Arch Intern Med* 2009; 169(2): 172-178). Of interest 3-29% of intubated patients develop a transient bacteremia with organisms usually found in the mouth, including *S. aureus.* (See Rijnders et al., Frequency of transient streptococcal bacteremia following urgent orotracheal intubation in critically ill patients, *Intensive Care Med* 2001; 27: 434-37; *Gerber, et al., Risk of*

bacterermia after endotracheal intubation for general anesthesia, Southern Medical Journal, 1980; 73(11): 1478-80)

Valdes, The incidence of bacteraemia associated with tracheal intubation, *Anesth* 2008; 63: 588-92
Konstantinou et al., Difficult intubation provokes bacteremia, *Surg Infect* (Larchmt) 2008; 9 (5): 521-4
In the same concept, A.J. Preston et al showed that 43% of elderly patients admitted to acute care hospitals carry gram negative rods in their oral cavities. No studies have examined the throat as a source for SSIs due to Gram negative bacteria. (See Oral Flora of Elderly Patients following Acute Medical Admission, See Gerontology 1999; 45: 49-52).

A 2015 Danish study showed that there are organisms present in the nasal microbiota below the culture threshold and identified only by finding their genes. Each 10 fold increase in *S. aureus* gene density increased the probability of a positive culture by 30%. So culture of the nares – an insensitive lab test- may underestimate true carriage of *S. aureus.*

Furthermore, in studies of bacterial genes the authors found distinctive prevalent bacteria not known previously to dominate the nasal microbiome including Proteus and Serratia (See Liu et al., *Sci Adv* 2015; e 1 400216). Some information suggesting an expanded role of the nares as a source of SSI, comes from the data of Phillips et al (Phillips, et al., Preventing Surgical Site Infections: A Randomized, Open-Label Trial of Nasal Mupirocin Ointment and Nasal Povidone-Iodine Solution, Infect Control Hosp Epidemiol 2014; 35: 826-32). The authors randomized 1697 patients undergoing arthroplasty or spinal fusion to topical chlorhexidine wipes with either twice daily mupirocin 2% ointment for 5 days prior to surgery or two 30 second applications of nasal povidone iodine 5% within 2 hours of incision. The study was an open label trial. In the intent to treat analysis, deep SSIs developed in 14 of 855 surgeries in the mupirocin group vs 6 of 842 in the povidone iodine group (p=0.10). *S aureus* developed in 5 of the mupirocin treated group vs 1 in the povidone iodine group (p-0.20). In the per protocol analysis, *S. aureus* deep SSI developed in the mupirocin group vs 0 in the povidone iodine group (p=0.03). Thus, if improved nasal decolonization is confirmed in further comparative studies of mupirocin vs alternatives, infection rates will be reduced further.

The new data are consistent with a broader role of the microbiome of the nose and pharynx in SSIs. So far no study has tried to reduce such carriage and examined the rates of subsequent infection.

Summary

The concept herein is that by controlling the microbiome of the skin, SSIs can be significantly reduced, and failure to control the microbiome will lead to SSIs. Note that the Darouiche study and the Tuuli study data indicate 40 – 45% incremental reductions of SSI, above a baseline from the use of standard povidone iodine skin preps and perioperative antibiotic use. http://www.bjjprocs.bone and joint.org.uk/content/go-b/jupp-1/140.4

The data on nasal carriage of *S. aureus* show a distinct link to *S. aureus* SSI and a significant reduction in *S. aureus* SSI if nasal decolonization occurs. Note that several studies have linked underlying diabetes or obesity with higher nasal carriage of *S. aureus* than those without such conditions.

Depending on the assumptions of the effect of povidone-iodine skin prep, a 40% incremental reduction in SSI, with chlorhexidine – alcohol plus ~ 10% (all *S. aureus*) current reduction in SSIs with mupirocin

plus chlorhexidine preoperative skin washes, the residual SSIs are 10% to 30% of the pre-povidone iodine effect. Such estimates suggest that at least 70% to 90% of the source of SSI can already be explained by studies of the patients' microbiome.

The plaintiffs have argued that a substantial proportion of SSIs arise from ambient air in the operating room. Current data suggest that reducing the microbiome counts on the skin with improved skin preps and removing the *S. aureus* burden in the nares accounts for 70%- 90% of the source of SSIs. The skin prep data are consistent with the concept that bacteria of the microbiome are already present in the wound soon after the incision during surgery, and there is no need to postulate an airborne rate. This concept is strengthened by the *P.* acnes data after shoulder surgery and after posterior spine repair surgery. The studies of the source of methicillin – resistant *S. Epidermidis* contamination of the sternal wound with CABG surgery also supports the microbiome of the skin as source of infection at the time of incision. Even with the best control of the microbiome available today, the majority of infections are endogenous.

V. Notes on Laminar flow and Rates of SSI

Laminar flow with reduced numbers of bacteria in the operating room air has been heralded as a strategy to reduce SSIs. This section examines the data.

In the remarkable study by Lidwell et al. who examined the effect of laminar air flow in operating rooms, he and his colleagues randomized 8004 patients undergoing THR or TKR. The risk ratio for infection was 2.6 favoring laminar airflow use (CI_{95} 1.8 – 4.2). However, the authors failed to control for the use of perioperative antibiotics which had an even higher risk ratio of 4.0 favoring use of antibiotics for preventing SSIs. (Lidwell, et al., Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: a randomized study, Br Med J (Clin Res Ed) 1982; 285: 10-14). See more detailed notes later.

Subsequently, three studies showed a worse outcome with the use of laminar air flow, more SSIs with laminar airflow:

1) Brandt's retrospective cohort (N=99,230).
   OR 1.63 for THA (1.06 – 2.52)
   OR 1.76 for TKA (0.80 – 3.85)

(See Brandt, et al., Operating Room Ventilation with Laminar Airflow Shows No Protective Effect on the Surgical Site Infection Rate in Orthopedic and Abdominal Surgery, Ann of Surg 2008: 695-700)

2) Gastmeier's Systematic Review
   (over 75,000 TKA and over 120,000 THA)
   OR 1.36 for TKA (1.06 – 1.74)
   OR 1.71 for THA (1.21 – 2.41)

(See Gastmeier, et al., Influence of laminar airflow on prosthetic joint infections: a systematic review, *J Hosp Inf*. 2012, 81:73-8)

3) Hooper's study of laminar air flow and space suits – 10 years' results of the New Zealand Registry
   (LAF in 36% and space suits in 24%)

(See Hooper, et al., Does the use of laminar flow and space suits reduce early deep infection after total hip and knee replacement, *J Bone Joint Surg. Br 2011; 93:85-90)*

Worse outcomes with LAF or space suits for SSIs

	Inf Rate	P
Space suits	.186%	
No space suits	.064%	<0.0001
LAF	.148%	
No LAF	.061%	<0.003
LAF and space suits	.198%	
No LAF and no Space suits	.053%	<0.001

An update on the New Zealand registry (Tayton E.R. et al., The impact of patient and surgical factors on the rate of infection after primary total knee arthroplasty, Bone Joint J 2016; 98-6: 334-40) reinforced the earlier message: Laminar flow systems appear to increase risk in TKA. A total of 64,566 TKAs were followed. The multivariate analysis showed that the OR for infection with the use of LAF was 1.6 (CI_{95} 1.04 – 2.47). They also saw an increase in SSIs at 6 months post operatively with use of surgical helmet systems. The data approached significance on multivariate analysis, with no significant difference at 12 months. The authors conclude that there "appears to be no significant benefit obtained from their use."

Peter Bischoff and colleagues preformed a systematic review and meta-analysis of LAF on SSIs (Bischoff, et al., Effect of laminar airflow ventilation on surgical site infections: a systematic review and meta-analysis, Lancet Infect Dis 2017; 17: 553-61). Eight cohort studies after THA (N=330, 146) showed an OR of 1.29 (CI_{95} .98-1.17 p=0.07 for an increased risk); and six cohort studies for TKA (N= 134,368) showed an OR of 1.08 (CI_{95} 0.77 – 1.52, p=0.65). They concluded that there is "no benefit for LAF vs conventional turbulent air in THA or TKA surgery".

An accompanying editorial concluded that "Until evidence is truly provided, the recommendations should not include LAF technology in operating rooms for prevention of SSIs (Weinstein, et al, Laminar airflow and surgical site infections: the evidence is blowing in the wind, Lancet Infec Dis 2017; 17: 472-3).

Of interest, Rabih Darouiche and colleagues performed a small prospective, clinical trial in which 294 patients undergoing total hip arthroplasty, instrumental spinal procedures or vascular bypass graphs were randomized to an air barrier system or not. The intervention shields open surgical wounds from airborne bacteria. There were significantly lower particulate and CFU densities in the intervention group. Furthermore, CFU density was significantly related to deep implant infections (p=0.021) but not to incisional infections. All four implant infections were in the control group. This study examined a small pocket of air close to the incision. An unanswered question is if the organisms come from the patient's own microbiome or possibly the OR team. Organisms found in the air were not analyzed to compare with those found in the implant infection (MRSA in 1, MSSA in 2, multiple species in 1). As a result, there was a correlation shown between numbers of bacteria in the air and the probability of deep SSIs. The data fail to show cause and effect, however. (Darouiche et al., Association of Airborne Microorganisms in the Operating Room With Implant Infections: A Randomized Controlled Trial, Infect Cont Hosp Epidemiol 2017; 38: 3-10).

If airborne contamination could be linked to implant infections, a critical question is whether a forced air warmer or a comparitor would increase airborne counts.

- Quite recently Oguz and colleagues examined airborne bacterial contamination during minor orthopedic surgery (N=80 patients). They randomized patients to either a forced air warming patients (Bair Hugger) or an electric warming system (Hot Dog). In a multivariate analysis, they showed that absence of laminar airflow and longer duration of surgery increased bacteria in the air significantly. However, the type of warming system had "no significant influence on bacterial counts on any sampling site." (Oguz R. et al. Airborne bacterial contamination during orthopedic surgery: a randomized controlled pilot trial. *J Clin Anesthesia* 2017; 38: 160-64).

The current data strongly support the patient's microbiome as the key source of SSI in clean surgery. There has been debate since the Lidwell study as to the route of infection of the wound. However, a large volume of data suggest that the airborne route is not important. A key factor relative to the Bair Hugger is the prospective study by Oguz and colleagues in clean orthopedic surgery comparing the Bair Hugger to the Hot Dog warmer. Warming with either device had no influence on bacterial counts at any sampling site.

Ayliffe and others have shown that bacterial counts in the operating rooms are directly related to OR activity (Ayliffe, C. A. J. 1991. Role of the environment of the operating suite in surgical wound infection. Rev. of Infec. Dis. 13(Suppl 10):5800-5804). Subsequently the CDC, Joint Commission and AORN have guidelines recommending restricted traffic in ORs, (Mangram, et al, Guideline for Prevention of Surgical Site Infection, 1999, Infect Cont Hosp Epidemiol 1999; 20: 247-80; Spruce, Back to Basics: Preventing Surgical Site Infections, AORN in 2014; 99: 600-611). Until recently many also argued for LAF, since LAF systems reduce bacterial counts. Just as the efficacy and safety of LAF systems have been challenged, so recently has the role of operating room traffic as a significant cause of SSIs have been challenged.

Bohl and colleagues performed a prospective cohort study of 1944 neurosurgical cases and a subsequent randomized single blinded, controlled clinical trial (N=1116) assigning half of the surgeons to regular traffic and half to a low traffic protocol (Bohl et al, The Barrow Randomized Operating Room Traffic (BRITE) Trial: An Observational Study on the Effect of Operating Room Traffic on Infection Rates, Clin Neurosurg 2016; 63; 91-95). In the cohort study, there was no significant difference in total door traffic route between the SSI and non-SSI group; paradoxically, there was a lower infection rate ($p<0.001$) with higher main-door traffic. In the randomized trial, the authors again found a paradoxical trend toward higher SSI risk in the low traffic protocol (3.2% vs high traffic 1.5%, p-0.06). The p value for "take backs" to the OR were respectively 3.1% vs 2.1% p=0.09). The authors concluded that the potential benefits of OR restrictions in reducing SSI rates in, at best trivial and is possibly nonexistent.

So far there are no compelling data linking airborne organisms in the operating room to SSIs. Four cohort studies and a recent meta-analysis show harm - not benefit - with the use of laminar flow systems. OR activity is linked to higher bacterial counts, yet a recent study shows paradoxical benefit with increased main door traffic. Further studies of traffic are needed to confirm the initial findings. A small study (4 deep infections) with a new device to control air near the operative site links bacterial and particulate counts to probability of deep joint replacement infection but no microbiological air and wound cultures were performed. A study of operative room bacteria in the air with Bair Hugger vs HotDog devices in orthopedic surgery shows no contribution to CFUs with either.

Early Studies on Ultraclean Air: Lidwell and Colleagues – 1980s

- Notes on Lidwell OM et al MS, "Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacements: a randomized study." (*Br Med J* 1982; 285: 10-14).

This was an ambitious study of over 8000 patients from 19 hospitals in England (n=11), Scotland (n=4) or Sweden (n=4). The study took 5 years to complete. Those operated in ultraclean OR air had a crude infection rate of 0.6% vs 1.5% in those in turbulent OR air (RR 2.6 and Cl_{95} of 1.6 to 4.2).

The study was flawed, unfortunately, with surgeons' optional use of antibiotics preoperatively, which had an infection RR of 4 (Cl_{95} 2.6-6.2): 0.6% infection rate with antibiotics vs 2.3% without perioperative antibiotics. In the turbulent OR only groups, the risk of infection without antibiotics was 3.4% vs 0.8% with antibiotics for a RR of 4.2.

From table 4- looking only at those patients in ultraclean OR air rooms there were 26 infected among 2120 (1.2%) not given antibiotics vs 20 of 5526 (.36%) among those on antibiotics, a RR of 2.41.

It appears that antibiotics had a greater impact than ultraclean air; yet ultraclean air plus antibiotics had a somewhat lower RR than turbulent air plus antibiotics 3.42 vs 4.2.

Other comments:

Much can change over a 5 year study period including improved technique, and the authors in the introduction note an attack rate for infection "as high as 10%: and with other surgeons very low. "The skill of the surgeons was not accounted for in this study." The timing of reported infections (month and year of study) would have been useful to know to see if skill improved over time. One hospital (in group 1) of the 19 hospitals accounted for one-third of all cases of sepsis, and in the entire study 40% of isolates were *S. aureus*. Thus, a common source outbreak or cluster might have accounted for the findings, which was not investigated.

There was no uniform method of random allocation (page 11).

- Notes on Lidwell O.M. et al MS: "Airborne contamination of wounds in joint replacement operations: The relationship to sepsis rates." *J Hosp Infect* 1983; 4:111-131.

A further analysis of the data from the 1982 publication focused on the correlation of the numbers of airborne bacteria and joint sepsis rates as well as correlations between the numbers of airborne bacteria and numbers of bacteria from wound washouts.

Approximately 20 air samples were taken at each of the 15 hospitals studied for each ventilation-clothing combination (ultraclean vs conventional, and conventional clothing vs body exhaust systems). This was ~ 10% sample of operations and 42 ventilation – clothing combinations. The authors lumped 6 to 9 of the 42 combinations into 6 groups. Thus, some surgeons and hospitals were represented in several of the 6 groups.

In each hospital the number of colony forming units was counted and the mean for each ventilation-clothing combinations noted. Subsequently, a geometric mean of the means was calculated for the 6-9 hospitals in each combination and used for the correlation with infection rates for each of the 6 groupings.

Crude correlations were made, and the authors performed a number of regressions to define the relationships arithmetically between the geometric means of airborne bacteria and the lumped infection rates of the 6 hospital groupings.

It should be noted that the geometric means were crude numbers and there was **no detailed study to show that any specific organism in the air was linked to an organism causing an infection in a specific patient.**

The bigger problem relates to the original flaw – failure to correct for the use of preoperative antibiotics, which could affect both the mean number of bacteria in the wound and in the air. The authors agree (p123), "the colony counts were also less when prophylactic antibiotics had been given," and also **(p126), "similarly, the reduction in the numbers of bacteria in the wash-outs associated with the use of antibiotics is similar to the 4:1 reductions in the incidence of sepsis among patients who received prophylactic antibiotics" (Lidwell et al 1982).**

There is an untested assumption in this paper i.e. that bacteria found in the air later fell into the wound. It seems possible that in operations where there are drills, saws, suctioning, and cautery, the organisms in the wound are splashed into the air. As such the control of the microbiome with perioperative antibiotics would have reduced the numbers of bacteria in the wound and thus subsequently, those in the air.

Other comments:

Though the authors predict that 90% of infections derive from the OR air, this has been easily discredited with current empirical studies. (See Bode et al *NEJM* 2010; 362:9-17 and Darouiche et al *NEJM* 2010; 363: 18-26). In their correlation model the number of organisms in the washout of the wound (W) is the sum of contamination (D) plus non-airborne contamination (K) plus the number found in the air (A). The authors never measured K and in the model assume it is low. Thus, A will be disproportionally high, yielding a falsely high ratio to W. Most importantly, **no infection dose was ever measured and no airborne count linked to specific infections**.

- Notes on Lidwell OM et al MS, "Infections and sepsis after operations for total hip or knee-joint replacement: influence of ultraclean air, prophylactic antibiotics and other factors." *J Hyg Camb* 1984; 93: 505-529.

The authors now focused on wound infection and sepsis not involving the joint, some differences in outcomes for knee vs hip surgeries, and the influence of underlying rheumatoid arthritis. 17% of patients had rheumatoid arthritis, but in 7/19 hospitals the prevalence exceeded 20% (maximum 34%) In the remaining hospitals (12/19) it was under 13% (low of 1%).

The authors state clearly (p.510), "Reasons have been given for believing that the apparent large reduction in the risk of joint sepsis was for the most part genuinely due to effects of antibiotics."

From Table 1:

Antibiotics in control group – 24/2968 became septic; antibiotics in ultra clean group – 9/1279 became septic (p value 0.85 not significant Fisher's exact test). Thus, so long as antibiotics were given, lower rates were seen compared with the no antibiotic group. However, no significant difference in antibiotic group with conventional air vs the antibiotic group with ultra clean air. Thus, no incremental boost was seen with ultraclean air.

Thus, the statement in the summary "the effects of ultraclean air and antibiotics were additive," (p. 505) is not substantiated. The authors also stated (p. 507), "the reduction in bacterial contamination of the wound due to a cleaner atmosphere and the increased resistance to infection from the use of antibiotics appear to combine together independently and multiplicatively."

A key point was made by the authors (p. 518), **"when followed by joint sepsis, the incidence of major sepsis for operations done without antibiotic prophylaxis was 7.9 times that for operations done with such prophylaxis; and the incidence for operations done in conventionally ventilated operating rooms was 2.8 times that for operations done in ultraclean air."**

	Antibiotics	No Antibiotics
Conventional Air	Major 0.6% Minor 3.7% Infection Rate	Major 2.3% Minor 5.1 % Infection Rate
Ultraclean Air		Major 0.7% Minor 5.2% Infection Rate

Thus, the role of major sepsis is the same in ultraclean air with no antibiotics as in conventional air with the use of antibiotics. It appears that ultraclean air had no effect on minor infection in the absence of antibiotics.

85 patients had "suspected joint sepsis" but were not re-operated on. Though the authors' surmise that the majority were in fact infected, clinical experience is that if infected, almost all would need reoperation in order to be cured.

S. aureus isolated in 258 cases

Phage typing in 115 of 258 cases

36/115 : matched the phage type of a person in OR

55/115 : no match with a person in OR

24/115: 18/nontypable with similar characteristics of those of people in OR

9/18 involved one surgeon

6/24 – possible match to a person in OR

A more detailed – examination in from table 8:

Of 115 *S. aureus* isolates:

23 were probably from patient (20%)

2 were probably from surgeon (2%)

11 were probably from assistants (10%) and an additional

6 were possibly from patient (5%)

9 ½ were probably from surgeon (8%)

8 ½ were probably from assistants (7%)

55 – no source found

Probably or possible from patient - 25%
Probably or possible from surgeon - 10%
Possible or probably from assistants - 17%

The authors found the risk of joint sepsis among rheumatoid arthritis patients to be double that for patients without rheumatoid arthritis. This was not corrected for in the primary analysis.

The authors state (p.522) that, "The outcome of the operation improved generally over the period of the study." The magnitude of the effect (p.527) corresponded to an average fall of ~ 50% from the first to third year.

It appears that the data show that ultraclean air influences only severe wound infections whereas prophylactic antibiotics influence both severe and milder infections (p. 525).

Of interest the authors state that the "use of cloxacillin or flucloxicillin alone did not appear to affect the incidence of joint sepsis associated with intestinal – type organism, but that this was reduced or eliminated when wide spectrum antibiotics were given…." In general, intestinal organisms are uncommonly found in the air. If cleaning the air was a critical factor, these intestinal organisms – assumed to fall into the wound from the air - would also be reduced. Instead, the data show that the patients' microbiome was the problem, that failure to control the intestinal organisms was the result of inactive preoperative antibiotics for these (Gram negative rods). On the other hand the antibiotics used would be expected to reduce Gram positive cocci e.g. staphylococcus and streptococcus and substantially reduce infections caused by these. This is exactly what occurred.

If patients develop a SSI after surgery including arthroplasty with organisms that comprise the normal flora of their skin and nares, for some reason their microbiome was not completely controlled. The next question is, can we differentiate the high risk patients for a SSI from those at lower risk. The discussion of risk factors for SSI follows.

VI. Risk Factors

a) **Markers of elevated rates of SSIs. Risk factors are those features of the patients or of the elements of their care that increase or decrease the expected baseline rate of disease.** They help explain the answer to the question, why do some people get an illness such as an infection and others do not. Risk factors are often identified by comparing those with an illness with those who did not acquire the illness in what are referred to as case - control studies. In such studies the cases and controls are examined for the potential risk factors in a defined number of days prior to infection in the case. In retrospective studies, they are quantified by *odds ratio* – a comparison of the odds of infection for example – among those exposed to "X" to the odds of infection among those not exposed to "X".

In the U.S., approximately 1 million patients undergo prosthetic joint implants each year and ~ 1% develop a prosthetic joint infection. Risk factors identify those at higher risk for a SSI. Once it is established that a risk factor for infection exists, efforts to reduce the exposure are made in attempts to minimize or eliminate the infection.

For decades, anesthesiologists have gauged a surgical patient's fitness for surgery using the ASA (American Society of Anesthesiologists) score preoperatively:

ASA Score

1. Healthy

2. Mild systemic disease (well controlled disease of one body system)

3. Severe systemic disease (controlled disease of more than one body system)

4. Severe systemic disease that is a constant threat to life

(See http://my.clevelandclinic.org/health/treatments - and procedures/regarding ASA score).

The Centers for Disease Control and Prevention (CDC) subsequently utilized the ASA as an element in their risk assessment for SSIs:

CDC NNIS Risk Index Score No. Points	SSI Risk	Criteria for CDC NNIS Points:
0	1.5%	1 – if contaminated or dirty surgery
1	2.9%	1 – if ASA ≥ 3
2	6.8%	1 – if op time exceeds the 75th percentile for that procedure (>3 hour for joint replacement)
3	13%	

See Pear SM. Patient risk factors and best practices for surgical site prevention managing. *Infect Control* 2007 (March):55-64

An ASA score >2 was also shown to be an independent risk factor for periprosthetic joint infection in a study of 9245 patients undergoing primary hip or knee arthroplasty – odds ratio 1.95 (CI_{95} 1-3.7) (L Pulido et al *Clin Ortho Relat Res* 2008; 466: 1710 - 15).

A Duke University case – control study of elderly surgical patients (age 65 or older) showed the following to be significant independent risk factors for a surgical site infection:

Variable	Odds Ratio (CI_{95})
Obesity	1.77 (1.34 – 2.32)
COPD	1.66 (1.17 – 2.34)
Contaminated or Dirty Surgery	1.65 (1.0 – 2.72)
Private Insurance	0.29 (0.12 – 0.68)

The study included 569 SSI cases and 580 controls; 18% had orthopedic infections. (Kay K. et al J Am Geriatr Soc 2006; 54: 391-396).

As an example of how to interpret the data is that the presence of obesity increased the risk for a SSI by 77% above the baseline. The statement that these are independent risk factors means that the estimates are already controlled for the presence of other potential risk factors, including COPD.

Infection of the Surgical Site after Arthroplasty of the Hip: Independent Risk Factors

Number of THA = 16,291
Rate of SSI = 2.23%
Ridgeway S et al J Bone Joint Surg (Br) 2005; 87: 844-50

Multivariate Analysis of Risk Factors for SSI

	Variable	OR	CI_{95}	P
Trauma	No	1		
	Yes	1.87	1.5 – 2.34	<0.001
Age	<65	1		
	65-74	1.13	.85-1.5	
	74-79	1.56	1.16 – 2.10	
	≥80	1.66	1.24 – 2.21	0.001
ASA	<3	1		
	≥3	1.55	1.29-1.88	<0.001
Duration of Surgery (Min)				
<60		1.04	.82 – 1.34	
60-90		1	Baseline	
90-120		1.23	.96-1.57	
> 120		1.58	1.23 – 2.03	0.004

Trauma, older age, higher ASA, and longer surgery time each predicted an above average risk for SSI.

Risk Factors for SSI

MA Olsen et al. Risk factors for surgical site infections following orthopedic spinal operations *J Bone Joint Sgy* 2008; 90: 62-9

Case Control Study
46 Infected and 227 uninfected controls: rate SSI – 2%

Independent risk factors

Risk Factor	OR	CI_{95}
DM	3.5	1.2 - 10
Preop Glucose > 125 mg/dl % or postop 200 mg/dl	3.3	1.4 – 7.5
Obesity	2.2	1.1 – 4.7
≥ 2 surgical Residents participating	2.2	1 – 4.7
Suboptimal timing of antibiotics	3.4	1.5 – 7.9

Key: DM= Diabetes mellitus
OR= Odds ratio
CI_{95}= 95 percent confidence interval

- This study is relevant to orthopedic surgery. With the presence of diabetes mellitus, a preoperative glucose over 125 mg/dL and obesity, a patient would have a higher than average risk of acquiring a SSI. Independent risk factors such as those found in a logistic model that are present in the same patient are additive. In this model such a patient would have a very much increased surgical site infection risk compared to patients without such risk factors by virtue of his diabetes mellitus, a preop glucose over 125 mg/dl and obesity. His risk would be 3.5 + 3.3 + 2.2 or 9 times greater than patients without any of these three risk factors.
- If the baseline rate of infection is 1% or 1.5% or 2%, that patient's predicted infection risk would be 9%, 13.5% or 18%, respectively – without considering other risk factors for infection.

Another case control study confirmed the importance of diabetes as a risk factor with an OR of 3.91 (P=0.04) Lai et al J arthroplasty 2007; 22:651-6

Importantly, Dowsey MM et al showed the outcome among patients who were both diabetic and obese in a study of 1214 consecutive primary total hip arthroplasties
Clin Orthrop Rel Res 2009; 467: 1577-81
Total infection Rate 1.5% (N=18)

Variable	OR	CI_{95}
Morbid Obesity	8.96	1.59 – 50.63
Diabetes	6.87	2.42 – 19.56
Men	5.93	1.95 – 18.04
Surgical Drainage	0.24	0.06-0.95

Of interest, there were no prosthetic joint infections (PJI) among diabetics who were not obese; 11 PJI if both diabetes and obese; 4 PJI if obese but not diabetic.

Smoking as a Risk Factor for Surgical Site Infections after Orthopedic Implant Procedures

Title: Smoking is a risk factor for organ/space surgical site infections in surgery with implant materials
Authors: F. Duran et al
Journal: int Orthop 2013; 37: 723-7

Largest orthopedic cohort studied: 17 French hospitals and 3908 patients; smokers comprised 16.4% and non-smokers 83.6%
59% THA and 30% TKA with 11% others

- Multivariate analysis of predictors for SSI in the 12 month follow-up: smoking had an odds ratio of 2.2 with CI_{95} of 1.4 – 3.7.

Comment: The model suggests that smoking, independent of other risk factors, doubled the baseline risk a surgical site infection after a joint replacement.

Alcohol Consumption and the Risk of Nosocomial Infections in General Surgery

Prospective study of 1505 patients Delgade-Rodriguez M. et al
BR J Surg 2003; 90: 1287-93

Men and heavy alcohol consumption
(Defined as over 108 Grams/d) increased the rate of all site nosocomial infections: Odds ratio 2.51 (CI_{95} 1.06 – 5.96), and in hospital Surgical Site Infections: odds ratio 2.16 (CI_{95} . 84-5.59 – NS)

Health Care Associated Infections in Surgical Patients Undergoing elective surgery: Are Alcohol Use Disorders a Risk Factor?

(de Wit, et al, Health Care-Associated Infection, J Am Coll Surg 2012; 215:229-36).

Over 1 million patients evaluated: Hospital acquired infections in 38,335 (3%); Surgical site infections in 0.5%
Alcohol abuse in 0.9% (11,640 patients)

Hospital acquired infections and Surgical Site Infections were strongly associated with heavy use, respectively:
Odds ratios, respectively of 1.7 and 2.73 ($P < 10^{-6}$)
Heavy drinking defined > 4 drinks/day or over 14/week for males

Comment: The data suggest a doubling of infection risk with heavy alcohol consumption alone.

In a study of comorbidities in patients with infected hip or knee arthroplasties, Lai and colleagues should that each of numerous medical comorbidities increased the risk of infection by 35% (OR 1.35 in univariate analysis); because this variable was linked to all other medical conditions, it was not entered into the adjusted analysis. In the latter the odds ratio for diabetes, an independent predictor, was 3.91 (1.06 – 14.44), p 0.041. (J Arthroplasty 2007; 22: 651-6).

CC Sheth and colleagues showed that alcohol and tobacco consumption affect the oral microbiome, specifically the carriage of *Candida Albicans* and *Streptococcus mutans*. (See Sheth, et al., Alcohol and tobacco consumption affect the orial carriage of Candida albicans and mutans streptococci, *Lett Appl Microbiol* 2016; 63: 254-9). Saliva samples of 105 patients were studies and patients stratified by duration and quantity of alcohol and tobacco consumption. Tobacco users harbored elevated levels of *C. Albicans* and alcohol consumption statistically significantly decreased the oral carriage of *S. mutans*. Such studies suggest that the microbiome is altered with some recognized risk factors for SSIs. More studies are needed on surgical patients, however.

In a cross sectional study of 20 women smokers and 20 women nonsmokers, RM Brotman and colleagues showed that smoking was linked to a lower proportion of vaginal lactobacillus species vs nonsmokers. That species has been thought to be part of a protective microbiome, and decline of lactobacillus carriage is linked to bacterial vaginosis. No surgical patients have been studied. (See Brotman, et al., Association between cigarette smoking and the vaginal microbiota: a pilot study, *BMC Infect Dis* 2014; Aug 28; 14: 471).

Risk Factors Identified Independent of the Bair Hugger Use

In the clinical trial using the Bair Hugger vs no Bair Hugger independent risk factors from multivariate analysis showed the following risk factors – after controlling for the use of the Bair Hugger (See Kurz, et al, Perioperative Normothermia to Reduce the Incidence of Surgical-Wound Infection and Shorten Hispitalization, *N Engl J Med* 1996; 334:1209-15).

Risk Factors	OR	CI_{95}
Tobacco Use (yes vs no)	10.5	3.2 – 34.1
NNIS Score (per unit increase)	2.5	1.2 – 5.3
Age (per decade)	1.6	1.0 – 2.4

In this study smoking, higher NNIS score and age were risk factors for infection independent of the use of the Bair Hugger. If a patient was a smoker, whether or not she used the Bair Hugger, she would have an odds ratio of 10.5 for infection. If the baseline rate was 1% or 1.5% or 2.0%, that person's risk for a SSI would be predicted to be 10.5%, ~16% or 21%, respectively, independent of NNIS score or age.

Infections with Prostheses in Bones and Joints - Review

Hematoma as an independent risk factor for prosthetic joint infection. A case control study Saleh K et al. J Orthoped Res 2002; 20: 506 – 15.
Study of THA (N=1181) and TKA (N=1124): 33 Infected Cases and 64 Controls.
Multivariate Logistic Regression.

Variable	OR	CI_{95}
Hematoma	11.78	3.02 – 46.03
Days of Drainage	1.32	1.08 – 1.62

Definition of hematoma: subcutaneous palpable collection of fluid or mass

- These data alone suggest that a patient with a hematoma increased his or her risk of infection ~12 – fold greater than patients without a hematoma.
- In this model the presence of a hematoma would predict a risk of infection of ~ 12%, 18% and 24%, respectively, if the baseline rate of infection is 1% or 1.5% or 2%, respectively. If one Thrombopophylaxis agent was more likely after THA or TKA to cause bleeding into a wound (hematoma), one would not be surprised to see an accompanying elevated SSI risk.

Surgical volume at an institution has been linked to risk of SSIs. Specifically, low volume hospitals have higher rates of SSIs, than high volume hospitals. In a recent report of Medicare patients undergoing THR from 2005-2011 with an annual number of replacements of 21,000/year, the relationship held:

THR Procedures/yr.	AOR (CI_{95})
1 – 24	1.58 (1.47 – 1.09)
25 – 49	1.34 (1.26 – 1.44)
50 – 99	1.22 – (1.15 – 1.30)
100 – 199	1.14 (1.07 – 1.21)
200 +	Ref

M. Calderwood et al Med Care 2017; 55: 179-85. These data suggest that patients' risk of a PJI increase as the number performed at a hospital declines. Best results were in institutions that did at least 200 per year.

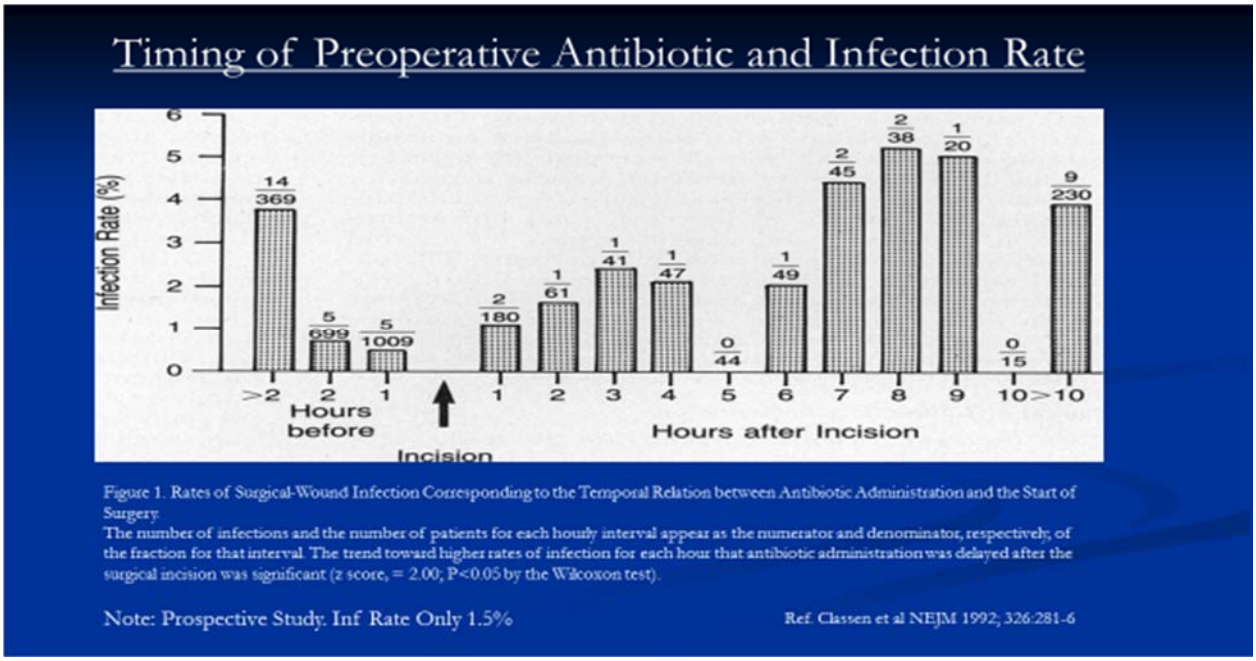


Figure 8

The timing of perioperative antibiotics has been shown to be important in preventing SSIs in general, with best results if given within 2 hours of the incision. (Figure 8)
(Classen, et al., The Timing of Prophylactic Administration of Antibiotics and the Risk of Surgical-Wound Infection, N Engl J Med 1992;326:281-6)

The key point is that getting the perioperative antibiotic timing right will reduce SSIs.

More recently most hospitals have targeted the 60 minutes before incision for receipt of perioperative antibiotics, and many in Europe target 30 minutes prior to incision

The data from Van Kastern et al suggest best results (lowest SSI) after THA might be 30 minutes prior to incision. (Clin Infect Dis 2007; 44: 921-7). (Figure 9)

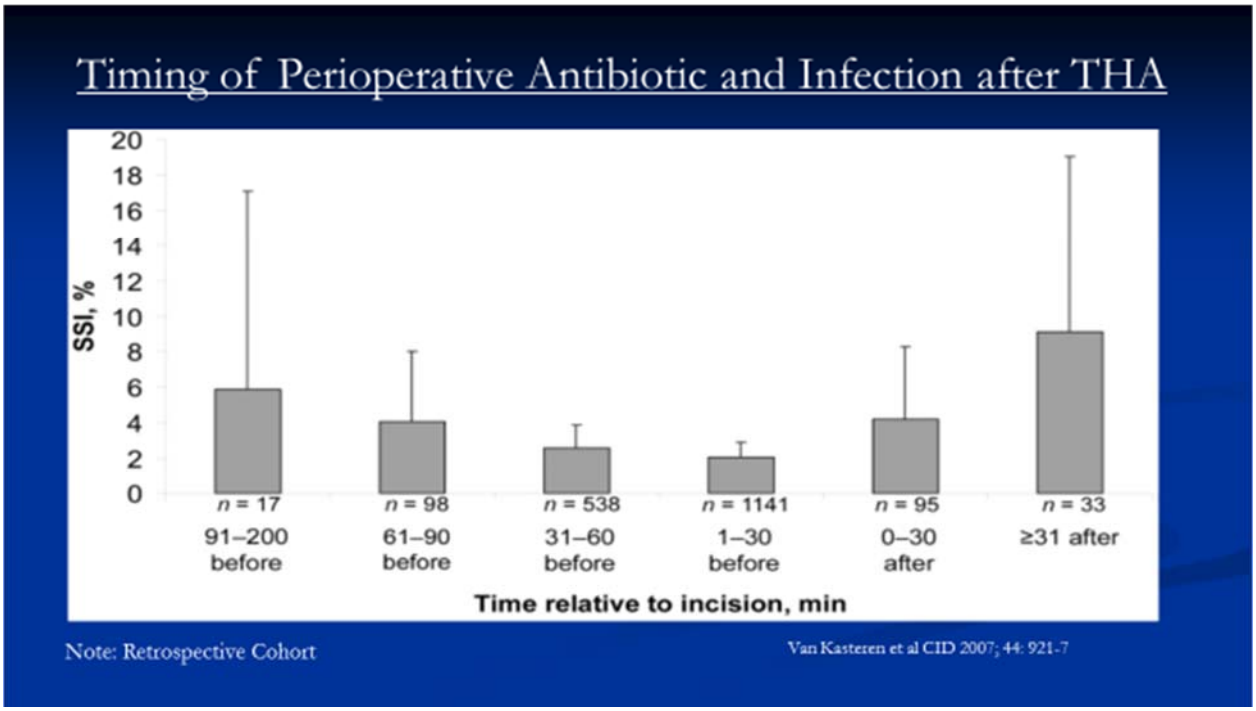

Timing of Perioperative Antibiotic and Infection after THA
SSI, %
20
18
16
14
12
10
8
6
4
2
0
n = 17
91–200 before
n = 98
61–90 before
n = 538
31–60 before
n = 1141
1–30 before
n = 95
0–30 after
n = 33
≥31 after
Time relative to incision, min
Note: Retrospective Cohort
Van Kasteren et al CID 2007; 44: 921-7

Figure 9

Risk factors for Prosthetic Joint Infections: Case-Control Study

Berbari, et al, *Clin Inf Dis* 1998; 27: 1247-54

Mayo Clinic Study by E Berbari: 462 cases matched to 462 controls

Risk Factor	Independent OR	CI_{95}
NNIS Score 1	1.7	1.2 – 2.3
2	3.9	2-7.5
History of same Joint Anthoplasty previously	2	1 – 4.3
Malignancy- not involving the index joint	3.1	1.3 – 7.2
SSI not involving Prosthesis	35.9	8.3 – 154.6

- With a patient's history of a prior hip joint replacement at the same site, this model suggests a doubling of the risk for infection – without considering other known risk factors such as obesity or diabetes.

  Controls were matched for age, sex, prosthesis location, and date of implantation. In addition, the length of follow-up for each control had to be greater than or equal to the interval from implantation to infection in the case.

  The odds ratios were derived from a conditional logistic regression model. Thus, the odds ratios are after a multivariate analysis.

  A recent study by Bedair and colleagues examined the question, if a history of treated prosthetic joint infection increases the risk of subsequent PJI at a different joint. A retrospective matched cohort study included 90 cases successfully treated for a second primary THA or TKA. Controls were matched for age, sex, diabetic status, BMI, ASA score institution, joint of interest and years of surgery (± 2). 10 of 90 controls vs 0 of 90 cases developed a PJI. The RR was 21 and CI^{95} 1.25 – 353.08, p=0.035.
  H. Bedair et al., A history of treated Periprosthetic Joint Infection Increases the Risk of Subsequent Different Site Infection. (*Clin Orthop Res* 2015; 473:2300-4).

Summary

A number of risk factors have been identified that address the question of why some patients get a SSI after the operation and others do not. Among those are preoperative diagnoses such as obesity, diabetes, nasal carriage of *S. aureus*, COPD, elevated preoperative or postoperative blood sugar level, smoking, and excess alcohol intake; and a post-operative hematoma. Process – related risk factors relate to surgeon and institution volume (number of THA and TKA performed per year), timing of perioperative antibiotics and preoperative skin preps. Some models include the presence of several risk factors, and the odds ratio of each patient can be added to get a summary odds ratio and multiply that number by the expected base line infection rate.

Note – Independent risk factors identify those patients having surgery who are at higher risk for a SSI than patients without such risk factors. It is likely that they alter the microbiome. Many surgeons try to control these by asking obese patients to lose weight before surgery, by asking diabetics to control their blood sugar before surgery, and ask smokers to stop smoking before surgery.

Though the science of the microbiome is young, a number of studies have shown changes in microbiome density and composition with the comorbidities listed above as risk factors. It should be emphasized that the presence of nasal carriage of *S. aureus* predicts a 2-3 fold increase in SSIs due to that organism. We know that obesity and diabetes mellitus both influence the microbiome by increasing the patients' prevalence of *S. aureus* carriage. Older patients have a higher carriage of Gram negative rods in their oral cavity, a possible source for SSIs. Some patients carry MRSA in the throat only, a possible source for SSIs and /or a marker of its presence on other parts of the body.

So far, the current data show remarkable safety of FAW including the Bair Hugger and no harm to patients. Current data make a compelling argument for the safety of the Bair Hugger. It is not a risk factor for infection. An unfortunate risk for patients undergoing arthroplasties is a prosthetic joint infection with an organism recognized to be a component of the normal microbiome. Progressive control of the microbiome has had a large impact on reducing SSIs. The currently uncontrolled residual risk of infection can usually be explained by risk factors listed above.

It is important to point out the multifactorial components of infection. Bacteria are a necessary but not sufficient cause. Risk factors address the components that increase risk for some patients. So if no bacterium and no risk factor is sufficient to cause an infection, all are in part risk factors that combine to cause an infection in some patients. If the question is what caused the infection in Mr. Jones, one could point to his organism recovered, his diabetes and obesity and say that all contributed, all caused the infection.

Risk factors thus play a role in SSIs by altering or increasing the bacterial burden in the microbiome and/or possibly by reducing the host's ability to resist her own microbiome or the bacteria from exogenous sources.

VII. Plaintiff's Critique of the Bair Hugger

a. Background – Routes of bacterial transmission from reservoir to operative site

The arguments have been made above for the key reservoir of bacteria implicated in clean surgery SSIs being the patients' microbiome – her own skin and mucous membrane flora.

The next question is how the organisms of the microbiome reach the operative site in most cases. Some possibilities include transient bloodstream infections of oral flora (including *S. aureus*) after intubation. A second possibility is the transmission of elements of the microbiome to the air in the operating room. A third possibility is that in most cases the offending organism is there at the operative site at the time of incision and causes infection directly.

In terms of nasal colonization with *S. aureus,* its presence may imply colonization elsewhere on the body, not just in the nares.

A clinical trial of the efficacy of mupirocin for clearing nasal carriage of *S. aureus* also examined hand carriage in the same people. Stable carriers of *S. aureus* were randomized for 5 days of intranasal mupirocin twice daily or placebo. At 3 months, 71% of subjects receiving mupirocin group remained free of nasal *S. aureus* vs 18% of controls. 30% of the mupirocin group and 50% of controls had *S. aureus* on their hands before initiating therapy. On day 3 of therapy, elimination of carriage was seen in 8 of 10 carriers on the hands of those receiving mupirocin, but only 3 of 16 were eliminated among those receiving placebo. The same fingerprint was noted in the nose and hands was noted in 97% of tests. Thus, a large proportion of nasal carriers have the same organism on the hands and elimination of nasal carriage was associated with elimination on the hands.

In terms of the transient bloodstream pathway, 3 – 29% of patients after intubation develop a bloodstream infection, and organisms could attach to the operative site at that time. Current data suggest the possibility but only a minority of infections seems likely in the face of current data.

In terms of the airborne route of transmissions, the arguments against this would be the finding of worse outcomes after the use of laminar airflow systems are in place – four large retrospective cohorts noted above and a recent critical review and meta-analysis. The studies in neurosurgery patients showing a decrease in SSIs with more main door traffic adds to the growing body of evidence against airborne transmission of the

microbiome. A recent contradictory study using an air shield over the operative site by Darouiche and colleagues – suggested this pathway, although no bacterial cultures of air and wounds were studied to show a true casual pathway. Importantly, a linked question is – if the airborne route of transmission occurs in a minority of cases, does the Bair Hugger increase the risk? In recent clinical trial in which the Hot Dog vs the Bair Hugger were evaluated, warming by either machine did not increase particle bacterial counts in the air in the operating room, suggesting no contribution by the Bair Hugger to risk.

A third possibility is that the organisms of the skin are currently not controlled maximally by skin preps or perioperative antibiotics, and the microbiome is already present at the operative site, causing infections in high risk patients. The data on the high risk of *P. acnes* after shoulder surgery and supportive data on posterior spinal repair surgery would strongly support this idea. The sternal wound contamination studies showing the skin over the sternum as the source of MRSE in CABG surgery further corroborates this concept. The point is that the organism causing contamination and infection of the wound are present at the time of the incision.

The 1963 study by Burke et al – well prior to the use of the Bair Hugger showed strains of *S. aureus* in the wound that matched those in the patients' skin, nose or throat, just prior to closing. These data also are consistent with the concept that the organisms causing infection after surgery are already present in the wound site and unrelated to the use of forced air warmers. These data are consistent with more recent data examining a marker organism, *P. Acnes*, in shoulder surgery (Joint replacement and rotator cuff repair) and posterior spine surgery. This species is commonly implicated in SSIs after the above procedures. Finding them before and immediately after skin preps and after incision and at the end of surgery is compatible with the idea that they are already in the wound at the time of the incision.

b. Particles, air bubbles, filter efficiency and cultures of the Bair Hugger apparatus.

Eight studies have been cited by the plaintiffs relating to the examination of air particles, air bubbles, filter efficiency of the Bair Hugger and cultures of the Bair Hugger. In these experimental studies **which were hypothesis – generation studies, no infection rates were measured, and no link of infection to the Bair Hugger was shown.**

Some studies showed increased numbers of bubbles and particles with the use of the Bair Hugger vs Hot Dog; some showed reduced filter efficiency, and some showed that the inside of the Bair Hugger apparatus had bacterial contamination. No study has shown bacterial contamination in the air from the blanket when the apparatus is in place as it is properly used for surgery. A brief summary of the studies follows:

Particles air bubbles, filter efficiency, cultures of Bair Hugger Apparatus

- Albrecht 2009 -25 FAW – using laser particle counts: 24% found to emit airborne particles. Microorganisms in 94% of internal surfaces; 34% filters had "abnormal" filtration

- Albrecht 2011 – 5 new and 5 used intake filters of Bair Hugger
  Filter efficiency 61% - 94% using sodium chloride aerosol
  92% microbes in air path
  58% generating airborne particles

- Reed 2013 – Intake filter was 64% efficient; swabs-100% FAW had bacteria. Hose end showed particles in 96%

- Legg 2012 – FAW caused increased temperature 1.1° C vs 0.4°C for the Hot Dog; and particles (1038 vs 273) over surgical site
  Volunteer patient in simulated OR with no OR "nurses"

- Legg 2013 – Simulated TKA in theatre. Buoyant helium bubbles counted: Increased particle counts and increased convection currents noted

- Dasari 2012 - Draped manikin in LAF room. FAW increased temp vs Hot Dog by 2.7° C and 3.6° vs resistive blanket

- Belani 2013 - FAW vs Hot Dog – with manikin in ortho OR. Increased neutrally buoyant bubbles with FAW

- McGovern 2011 – Increased bubble counts over surgical site greater with FAW than with Hot Dog and air from floor mobilized

In Mr. Albrecht's deposition , he clarifies his many studies, stating that the airborne particles counted do not reflect bacterial counts (p.65-66); that particles counted out of the Bair Hugger were noted, but not much in the way of bacteria was noted (p 73); that filtration efficiency was based on particle counts coming and leaving but not bacterial counts (p. 103); that in the 3 Minnesota hospitals he and his colleagues found particle emissions with varying efficiency of the Bair Hugger filter and internal surface contamination, but "none looked at the actual bacteria in the airstream." (p.103-104). The table below summarizes the emissions from the unpublished Bair Hugger studies in Minnesota (p. 110):

Institution	Tested No. Units	No. CFU Cultured
St. Cloud	3	0/3
Alexandria	3	6 measurements: 2 had 1 CFU 4 had 0 CFU
Regina	3	9 Measurements: One unit had all zeros Another unit had 1 cfu and 0s in the others Another unit - had 1 cfu on one and two zeros

Mr. Albrecht – in response to why these data were not included in the published studies - says that since the ORs studied were at rest, he and his colleagues were unsure how to interpret the results (p. 113). Two additional studies were also conducted by Mr. Albrecht that were not published. They also showed that no bacteria were noted when the Bair Hugger was in use. Thus, five negative studies were not published (Augustine deposition, pp 53-75 re: Exhibit 8). The question was: "so does this comport with your recollection back in 2007, 2008 time frame, internally Augustine Biomedical + Design tried five different times to capture viable bacteria coming out of the airstream from the Bair Hugger hose, but – and using three different capture techniques, but never captured any meaningful numbers of bacteria?"

Answer: "That's what these reports say" (p. 68).

In Mr. Legg's deposition he added new information related to his particle studies. He and his colleagues attempted to measure bacteria using agar plates in the simulated operating room experiment (p. 53). Specifically, they used agar plates "placed where we were concerned, which was on the surgical site" (p. 54). When asked how many bacteria grew, he responded "less than one" colony forming unit (p. 55), during the time when the Bair Hugger was used. When asked why this information was not reported with the report about the particles, he said that "it didn't really add anything" (p. 5). He later clarified that the standard – set for the orthopedic theatre – is also less than one colony forming unit. When asked to respond to the finding that despite increased particles being mobilized at the operative site, the particles were not adding to the bacterial load, Mr. Legg agreed (p. 58).

In his deposition, Dr. Paul McGovern provided raw data on a number of studies in which attempted to count bacteria or particles in the air of an operating room (volume 8 pp 3539 – 3717) at Wansbeck General Hospital. In 4 experiments the introduction of a surgeon raised the particle count in the zone of the operative field, most marked when the surgeon touched the disinfected skin within the field. "However, there is no suggestion from these results that turning on the Bair Hugger makes any difference to the operative field particle counts" (p. 3547).

Minimal numbers of bacteria were isolated from settle plates opened for 4 hours. Counts of microorganism from settle plates showed mostly zeros (p. 3548). Air samples during the operating procedures also showed zero cfu when the Bair Hugger was turned on (p. 3550). Wound swabbing and sampling Bair Hugger showed "only very low numbers of skin bacteria" (p. 3552). He concluded (p. 3574) that "Use of forced air warming devices does not increase the bacterial count in the vicinity of the operative field."

These data on bacterial counts were never published, and Dr. McGovern and his colleagues chose to pursue studies of particles and had the selective data from the latter experiments published. Asked why the different approaches, Dr. McGovern said that an abstract had been rejected (deposition p. 67), that negative findings are difficult to get published (deposition p.68), and that no statistical significance of the data was taken into account (deposition p. 71).

One is forced to conclude that a large volume of data had shown that the use of the Bair Hugger has no influence on bacterial counts in the operating room. The authors of these studies failed to publish the data and instead appeared to focus on air currents and particles as implied surrogate markers of bacteria counts.

c. The McGovern Study – The Clinical Arm

The McGovern study (*J Bone Joint Surgery* (BR) 2011; 93: 1537-44) is cited by the plaintiffs as a clinical evaluation of the comparison of the Bair Hugger vs the Hot Dog Warming devices with the end point of the rate of prosthetic joint infections. The abstract states that there was an "elevated infection odds ratio of 3.8 (p=0.024)" favoring the use of the Hot Dog.

These were a number of fatal flows in study design and analysis, and **the authors themselves correctly state that "this study does not establish a casual basis for this association."**

The study was a "before and after" observation comparing surgical site infection rates between the Bair Hugger and Hot Dog systems. The method section offers no hypothesis, no study design details to offer a rationale for the study periods for the two warming systems. The authors acknowledge the failure to control for independent risk factors: blood transfusion,

obesity, incontinence and fitness for surgery. They also ignored multiple other factors known to affect infection risk.

Other shortcomings include the following.

- Intraoperative temperatures were not measured, thus a key risk factor was not examined.
- The surveillance systems – case finding methods – were not mentioned, and there are no data on validity of surveillance or in completeness of case finding after patients were discharged. This is especially important in non-contemporaneous comparisons, where observation bias can be introduced.
- There were no data to show that perioperative antibiotics were appropriately timed relative to the incision in the two time periods.
- With the large number of *S aureus* isolates recovered during the forced air period (N=11) vs none (N=0) for the conductive fabric warming, one needs to know what workup was done to rule out an epidemic caused by a single clone. No fingerprinting of isolates was noted.
- One of the coauthors, Mr. Albrecht, worked for the company competing with the Bair Hugger and has a substantial conflict of interest.

An important point with respect to controlling for such confounding factors is that the odds ratio reported is a univariate funding, not corrected for the known confounders of infection. It was not a multivariate analysis but instead a crude examination of incomplete data.

Even more serious flaws involve bias (systematic errors) in the study, which – unlike confounders – cannot be corrected. Bias in a study is a fatal flaw. There were multiple biases in the study, each one of which favored the Hot Dog:

1) Rivaroxaban (Xarelto) anticlotting drug – linked to wound hematomas – was used for part of the Bair Hugger period but never during the Hot Dog use period; (See Professor Holford's analysis).

2) Gentamicin perioperative prophylaxis alone was used for much of the Bair Hugger period yet two antibiotics – gentamicin plus Teicoplanin – were used always during the Hot Dog period. Gentamicin would be expected to have no or little activity for MRSA and for coagulase negative staphylococci. Dr. Reed and co-authors from the Northumbria Healthcare NHS Foundation Trust wrote that "gentamicin 4.5 mg/kg alone should not be used as prophylaxis for primary joint arthroplasty as it…increases the risk of other postoperative complications" increase in pneumonia..acute renal failure requiring HDU admission..and rate of return to theatre." The authors noted trends of increasing resistance to gentamicin among the coagulase negative s*taphylococc*i. In conclusion, they say "we have changed our prophylaxis to low dose gentamicin (3mg/kg) combined with Teicoplanin 400 mg given once."

Sprowson A et al. Changing antibiotic prophylaxis for primary joint arthroplasty affects postoperative complication rates and bacterial spectrum. *The Surgeon* 2013; II: 20 – 24.

It should be noted that the study extended over a 2-1/2 years period during which time 20 months were exclusively for the Bair Hugger followed by an optional warmer for 3 months of transition, then followed by a 7 months exclusive period of use of the Hot Dog. This is a very strange study design, suggesting a late decision to examine data retrospectively.

3) In the Bair Hugger period there was no MSSA screening from 7/01/08 through 12/31/10 (Dr. Reed's deposition page 110), during which time there were 9 pure plus 1 mixed *S. aureus* infections. There were no MSSA in the Hot Dog study period.

MSSA screening began in January 2010 and was continued thereafter, including the entire Hot Dog period.
A systematic review of *S. aureus* screening and decolonization in orthopedic surgery involving 19 studies showed a reduction of SSIs or wound complications in all 19 (Chen et al Clin Orthop Rel Res 2013; 471: 2583 – 99). Nine of the studies were prospective and 10 were retrospective. Most studies evaluated patients undergoing elective joint replacements.

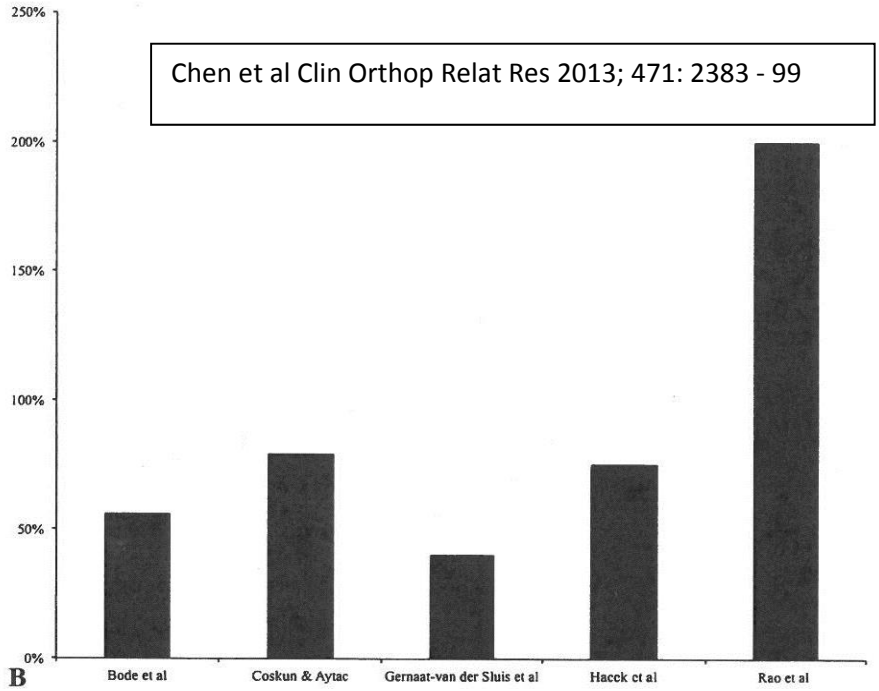
The reduction of overall SSIs ranged from 13% to 200%; the reductions of MRSA SSIs ranged from 29% to 149%; and the reduction of *S. aureus (MSSA)* SSIs ranged from 40% to 200%. Four of the five studies evaluating *MSSA SSIs showed* ≥ 50% reduction of *S. aureus* SSIs.

Based on the studies above, it is reasonable to suggest that in Bair Hugger period there could have been on the order of a 50% reduction of MSSA SSI, from 10 to 5, had MSSA screening been instituted from 7/01/08.

Figure 10

Chen et al Clin Orthop Relat Res 2013; 471: 2383 - 99

Percent MSSA SSIs reduced with MSSA screening



During the Bair Hugger period, there was a THA infection related to *Pasteurella Multocida.* The procedure date was 12/09/08. This was surely community acquired and had nothing to do with what occurred in the operating room. A review of the literature would support dropping this case from the Bair Hugger health care associated infections. Sixteen cases of TKA and two THA sepsis have been reported in the literature almost always caused by a dog or cat bite, scratch or tick. These are most commonly linked to a bacteremia.

Hydeman J et al
Internat J Infect Dis
Acute infection of a total knee arthroplasty caused by Pasteurella Multocida, a case report and a comprehensive review of the literature in the last 10 years.
Before examining methodological study issues, one should drop the case of Pasteurella and correct the misclassification (once fewer in the Bair Hugger period and one more in the Hot Dog period) as noted in discovery.

4) A switch to chlorhexidine – alcohol skin prep was made on October 1, 2010, so only during the Hot Dog period. Since it has been clearly shown that this prep leads to a 40% reduction in all SSIs, a serious bias is present. A 40% incremental reduction in SSIs during the Bair Hugger period would have had an enormous decrease in the infection rate.

In the manuscript that was published, the authors had an illustration of infection rates. The impression was a flat rate over the first 20 months (Figure 11).

FORCED-AIR WARMING AND ULTRA-CLEAN VENTILATION DO NOT MIX

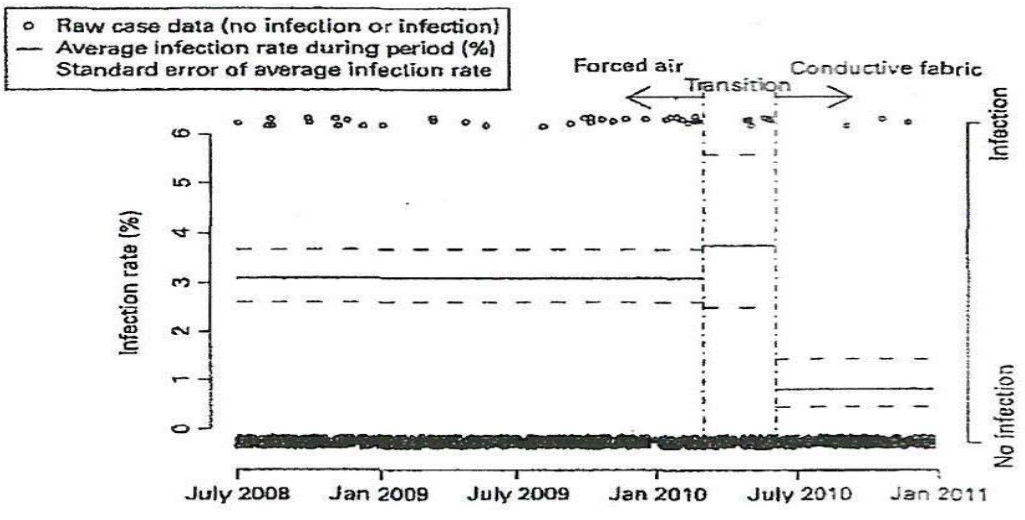


Fig. 7

Graph showing time-based trends of joint sepsis rates for hip and knee replacement cases. The outcome of each individual case is plotted on the right-hand axis (data are jittered to avoid overprinting). The infection rates for each period (forced-air, transition or conductive fabric) are plotted on the left-hand axis. Standard error of the mean was estimated using logistic regression.

Figure 11

A confusing finding is the more explicit but unpublished information on surgical infection rates over time, showing a progressive decline in rates over the first 8-12 months of the Bair Hugger period (Figure 12) followed by a later rise. If the Bair Hugger truly caused infection rates to rise, one would not expect a continue trend downwards as they were in use. The inconsistency is unexplained and suggests something else happened late in the Bair Hugger period to increase rates.

Further confusion related to the fall and later rise of rates in the Bair Hugger period relates to the fact that the authors had data for 9 months prior to the official study beginning. With the use of the Bair Hugger for these months, the infection rate was 0.68%, very low.

In contrast to the curve above (Figure 11) that was published – showing a flat line for infection rates during the Bair Hugger period, the true curve (Figure 12), showed an impressive decline with the Bair Hugger followed by a dramatic rise. One can only conclude that the latter was meant to obscure the raw data. It would have the effect of misleading the reader.

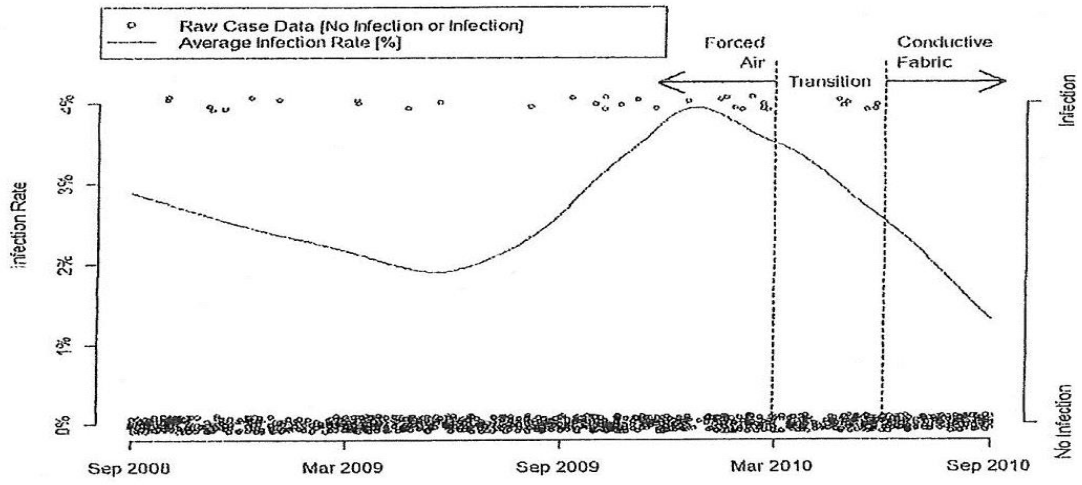


Figure 12

Figure 7: Infection data for n=1290 joint replacement cases with the outcome plotted on the right hand axis (data is jittered to avoid overprinting). A moving average of infection rate was plotted on the left hand axis. The change from forced air to conductive fabric patient warming in the orthopedic theaters is identified along with the transition period where both systems were used.

Given the unusually high rate of infection rate in the Bair Hugger era and the large proportion of *S. aureus* isolates recovered, some analysis by the hospital's infection control team a medical microbiologist or risk management office should have occurred. The microbiologist might have done finger printing of all *S. aureus* isolates to see if a single clone was dominant, indicating a common source problem. A review of OR procedures, perhaps some case control studies and interviews would all have been completed. The absence of such inquiries and analyses suggest a lapse in standard hospital safety.

The figure below shows the study design and highlights the known biases introduced over the 2-1/2 ear period of observation. (Figure 13 provided by Dr. Jonathan Borak)

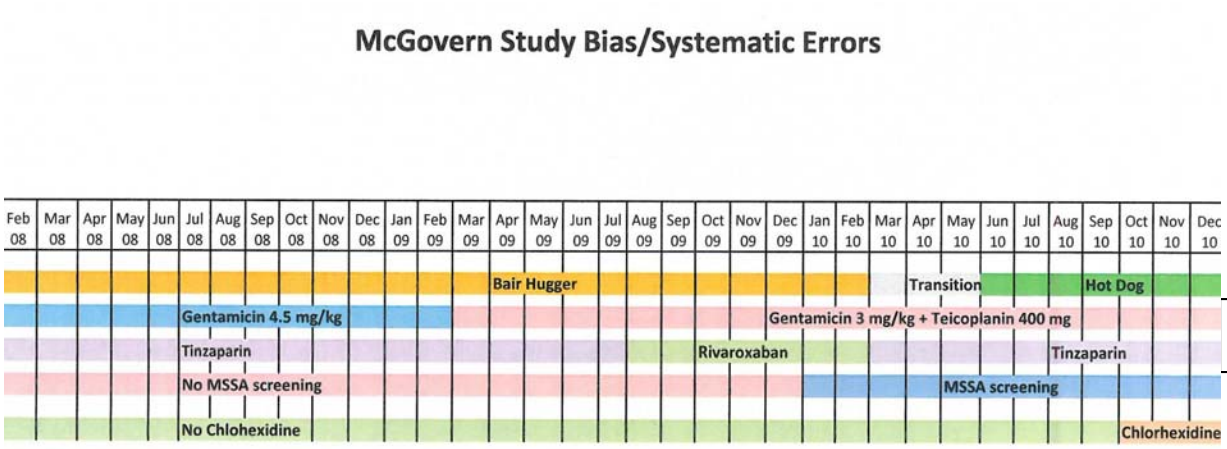


Figure 13

Some insight into a key change in standard patient management is provided by Dr. Mike Reed, consultant orthopedic surgeon at Northumbria Healthcare (*November 2011. The Clinical Services Journal. Infection Control in Orthopedic Surgery*). He stated in the article that he moved away from the traditional aqueous povidone – iodine skin prep to chlorhexidine alcohol. This change occurred in October 2010. That would favor a much lower rate of SSIs during that period late in the study. He also states that the "infection rate doubled when using gentamicin prophylaxis", the drug used exclusively during the Bair Hugger era. A possible cause for failure, prompting the change, was resistance to gentamicin by MRSA and coagulase negative staphylococci.

5) Further insights into the study flaws that failed to keep a level playing field were provided by Julie Gillson and Gail Lowden, who summarized the various protocol changes instituted by the Northumbria Healthcare NAS Foundation Trust (site of the McGovern study) which corresponded to reduced orthopedic SSI rates (5% to 0.9%) over time (The Clinical Services Journal. Ochler 2014. pp 71-74. See http://www.clinicalservicesjournal. Com/Handlers/FileHandler. Ashx? Fileld = 13230).

Such changes included – in 2008 – the identification of patients readmitted with an SSI; in early 2009, two full time SSI nurses were appointed to improve case finding and initiate "a robust and prospective surveillance; introduction of an SSI bundle in 2009, which included the introduction of octenisan antimicrobial skin washes preoperatively at home for all elective THR /TKR patients; subsequently OR disciplines were instituted limiting the number of people entering the OR area, no use of personal clogs, use of appropriate time of perioperative antibiotics and others. It is likely that hospital personnel became increasingly aware of the special focus on preventing orthopedic implant related infections. As a result, a "Hawthorne effect" would be in play, in which behavior changes occur among people who sense increased attention to their work activities. The Hawthorne effect is a form of confounding which can

improve work outcomes. Since the many protocol changes occurred late in the McGovern study, a Hawthorne effort for reduced infectious during the Hot Dog period would be expected. In the July 2012 issue of the Operating Theatre Journal, on (page 10) "Kimberly – Clark announces winners of inaugural HAI watchdog awards", championing infection prevention in UK hospitals:

"The winner of the category for operating theatre infection prevention initiative was Northumbria Healthcare NHS Foundation Trust which made a pledge to drive down surgical site infections (SSI) in Orthopedic Surgery."

They list the changes as employing two dedicated SSI surveillance nurses an a range of initiative in theatres including "restricting access to the department, screening patients for potential infections before they come into the hospital and improving skin preparation." They do not mention anything about use of the Hot Dog warming system.

In a crude subset analysis to provide insight into the observed effect during the Bair Hugger vs Hot Dog study periods, author and statistician Mr. Albrecht said that when rates of infection were confined to periods when the antibiotics and thromboprophylaxis drugs were the same, there was no significant differences ~ 1% for the Bair Hugger and 1% for the Hot Dog period (Albrecht deposition, pp 197-200).

Furthermore, when the infection rates were compared for the two devices (Bair Hugger vs Hot Dog), the rates were 4.3% for the rivaroxaban period vs 1.2% for the Tinzaparin period – when the antibiotics were held constant. The data illustrate the high risk of infection after rivaroxaban, a thromboprophylaxis drug never used in the Hog Dog period but on in the Bair Hugger period.

The McGovern study should be entirely discounted because of so many failures: it did not correct for numerous cofounders, was laced with several biases, and failed to establish a clear definition of case finding and show any independent validity of case finding methods to their recorded infection rates. The authors acknowledge that a causal relationship cannot be shown with this manuscript.

VIII. Investigating the Cause of a Cluster of Infections

A valid methodology exists to examine the cause of a cluster or epidemic of infections. When the rates of infection exceed a background threshold, a case control study is performed in which the exposures and experiences of infected cases are compared to appropriately matched uninfected controls. So the first step is to show statistically that the current rate exceeds background rates.

Once a difference in infection rates (baseline vs current) is found in exposures or experiences, statistics are applied to see if the differences are significant. Afterwards microbiological

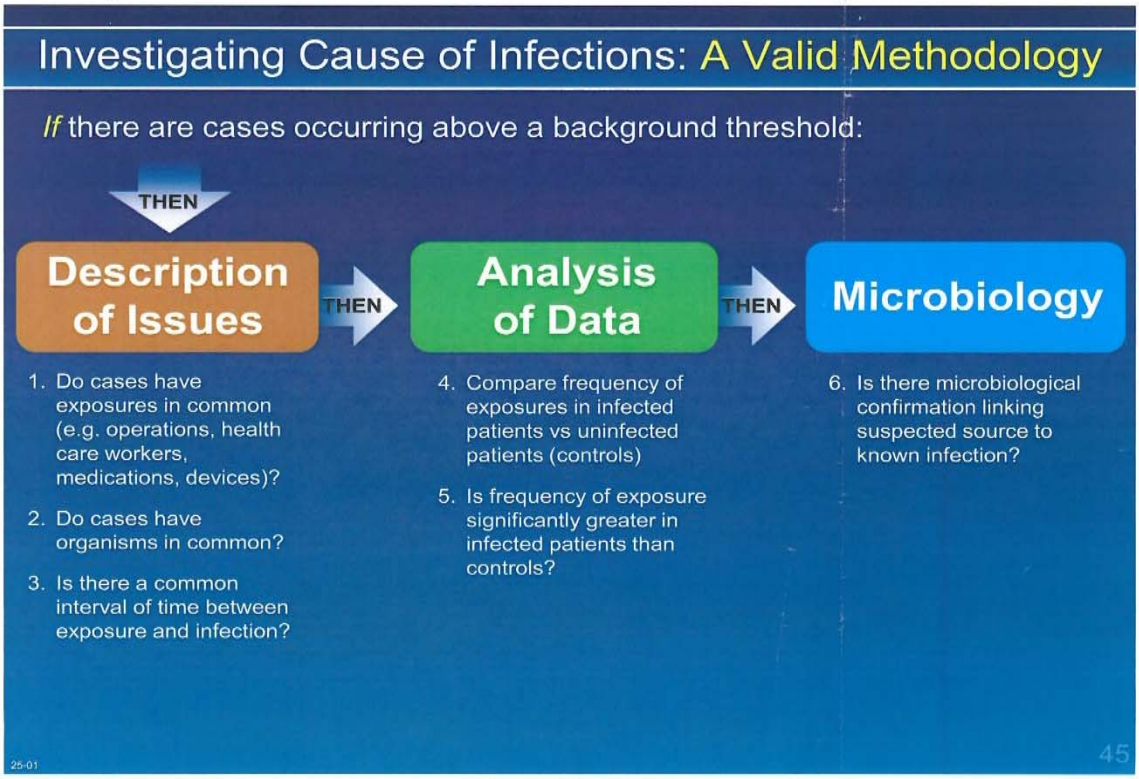


Figure 14

confirmation is sought to show that the exposure or experience was in some way linked to the same organism as encountered by the patient. (Figure 14).

If a single patient acquires an infection, in contrast to a cluster, there are limits to investigating the cause of that infection. Specifically, if the surgical site infection is not part of a cluster, if the bacterium implicated is commonly found on the microbiome, and if the investigation is not close in time to the date of surgery, then there is no significantly valid methodology to identify the source retrospectively. The most likely cause – the patient's own microbiome that was not adequately controlled – cannot be ruled out. The infected patients were most likely "pushed over the line" by their underlying risk factors.

Note that step 1 has never been shown – there are no regional, Statewide or National data to show a link between use of the Bair Hugger and a significant increase in SSIs. National trends corrected for confounders, show the opposite – a reduced rate of SSIs after THR and TKR during the Bair Hugger Era. The organisms implicated in infections are part of the microbiome of surgical patients. Infections afer surgery can often be explained by the underlying contribution of risk factors.

IX. Summary of the Report

A large number of patients who have undergone either a total knee replacement or total hip replacement have filed suit against 3M after they developed an infection of the prosthesis. The bacterial isolates identified in the many microbiology laboratories have varied, and no single organism with a unique fingerprint was demonstrated for all.

The patients with prosthetic joint infections live in several states in the U.S. and had surgery in many hospitals. Importantly, the plaintiffs have provided no data to show that an outbreak occurred at any hospital, in any state, or widely in the U.S. and traced the statistically elevated SSI rates to the Bair Hugger. Thus, they have not provided the first step in an investigation – show that an epidemic or unique cluster exists.

Those infected have alleged that the cause of their infection related to the use of peri-operative Forced Air Warming device called the Bair Hugger. Their hypothesis is that air currents in the operating room bring floor organisms up near the operative site, where they fall and incite the infection, and eventually lead to elevated infection rates.

The plaintiffs rely heavily on a single retrospective study by McGovern and colleges which purports to show an advantage of the Hot Dog resistance warming device to the forced air warming device – the Bair Hugger. The McGovern study team said in their publication that their data – showing fewer infections with the Hot Dog device - do "not establish a causal basis for this association." This is an appropriate statement, given the many flaws in study design, including a series of issues: Lack of case finding methods and validity, failure to control for numerous confounders, and introduction of several biases favoring the Hot Dog device. There is also the problem of a before – after design that did not allow for concurrent controls during the 2 ½ year study duration. Furthermore, one of the authors works for the competing company and thus has a significant conflict of interest.

In contrast, the Bair Hugger clinical trials utilized concurrent controls. Each study was prospective, with blind assessment of outcome and randomized. The two widely-cited clinical trials show statistically significant benefit for the Bair Hugger in reducing surgical site infections. These clinical trials are also supported by data from a meta-analysis, six cohort studies, an independent review by the ECRI institute, a case control study and U.S. national trends from the Centers for Disease Control and Prevention showing falling rates of infection in the Bair Hugger era after joint replacement. Furthermore, eight microbiological studies show no signal for harm from the Bair Hugger.

Current data suggest ~ 1% risk of infection after a THR or TKR with causative organisms that comprise the normal flora of the skin or nares, the microbiome of the skin or nasopharynx. Control of the microbiome – in the Bair Hugger era - has improved greatly in recent decades

due to the use of perioperative showers, nasal decolonization of *S. aureus,* improved skin antiseptic preps, warming, and others. Yet some patients still become infected. For the most part those infected are different from those not infected by virtue of comorbidities – conditions that increase the risk a priori for a SSI. These include obesity, diabetes mellitus, smoking, carriage of *S. aureus,* excessive alcohol intake and others. Current data support an altered microbiome in these comorbid medical conditions different from the normal microbiome.

The plaintiffs have presented eight manuscripts showing an increased temperature, particles or bubbles with the use of the Bair Hugger vs the Hot Dog, and showing some positive cultures of bacteria in use Bair Hugger devices. None indicate a relationship between Bair Hugger use and any infection. There might be viewed as hypotheses – generating studies, yet all true patient studies and microbiological data support the safety of the Bair Hugger. In the discovery phase of the trial, it has been shown that 7 studies showing safety of the Bair Hugger were not published, were kept secret.

An incontrovertible amount of data from the literature support the patient's own microbiome (flora of skin and nares) as key sources of the bacteria causing SSIs. Studies show that control of the microbiome by improved pre-surgical skin preps and use of effective nasal decolonization substantially reduce the SSI rate.

A debated question is how organisms get to the wound site from their microbiome reservoir on the skin and nares if the microbiome is not controlled. Possibilities include transient bacteremia after intubation; direct movement during surgery of the flora of the skin by instrumentation or hand carriage of the surgical team; some movement of the flora from the skin or nares to the air. Nasal carriage however is a marker of carriage elsewhere on the body. Organisms found in the nares are often found in the groin, perineum and axilla. The plaintiffs argue that the airborne route is key, citing the original studies by Lidwell and others. That study was flawed by not taking into account the use of antibiotics which had a higher effect (odds ratio) than the use of laminar air flow. Many hospitals introduced laminar air flow into operative suites after the Lidwell studies, however. The hypothesis is that SSI rates would fall and the reason they would fall was that the airborne bacterial load was reduced. However, four very large retrospective cohorts involving over 300,000 patients showed higher rates with LAF. A 2017 publication of a meta-analysis shows no benefit of LAF.

A recent study using a device to create a barrier to airborne bacteria did show a correlation but no cause effect could be established. So a question arises, does the Bair Huger influence the numbers of bacteria in the air of the operating room. A recent randomized study of air bacterial counts with the Bair Hugger vs the Hot Dog showed no influence of either warmer on the airborne number of bacteria.

I disagree strongly with the testimony of Dr. Jarvis, expert witness for the plaintiffs. In his deposition he correctly outlines the approach to an outbreak of infections (p.3) and concludes from his experience: "Our team's outbreak investigations established that culture surveys of personnel or the environment without a prior epidemiological investigation can be misdirected, expensive, or a waste of laboratory resources and therefore should not be performed before comparative epidemiological studies are completed. Our team's approach of integrating epidemiology and microbiology remains vital to conducting a successful outbreak investigation. The combined epidemiological – laboratory investigation approach has become the "gold standard" methodology…"

He then cites the correct epidemiological approach used in the Heater-Cooler outbreak due to *Mycobacterium chimaera*. Yet he ignores the fact that no such gold standard approach has been conducted to show that any outbreak exists with use of the Bair Hugger device: no increase in rates of SSI have been demonstrated as step 1 of a careful epidemiological investigation.

The plaintiffs have cited the clinical arm of the McGovern study as critical to their arguments. Yet Dr. Jarvis offers a superficial, single sentence mention (p. 12) that is uncritical and incomplete.

While focusing on pre-clinical studies of the Bair Hugger, Dr. Jarvis ignores a vast body of clinical studies showing the safety of the Bair Hugger: The second clinical trial (Melling), historical cohort studies, the case control study and national data infection rates in the era of the Bair Hugger.

His statement (p. 5) that "exogenous sources account for the majority of SSIs", is unreferenced and ignores the vast number of studies showing just the opposite – most are in fact endogenous.

Dr. Jarvis' deposition is superficial and wanting.

The overwhelming clinical data, national trends data during the Bair Hugger era and microbiological studies attest to the safety and benefits of the Bair Hugger.

I also disagree with Dr. Samet's testimony. His focus on the McGovern study is at face value and as a result is uncritical. His bias is illustrated by the gratuitous statement (p. 11) that concerns about confounding are "typical general claims made by those seeking alternative explanations for an association, and reach back to the strategies employed for decades by the tobacco industry".

Dr. Samet takes the univariate odds ratio of 3.8 in a flawed study at face value, stating that its size makes "confounding…unlikely… and not supported." He ignores the bias related to MSSA screening during the Hot Dog period and ignores the high numbers of *S. aureus* recovered in the Bair Hugger era and none found in the Hot Dog era after the initiating of MSSA screening in January 2010.

He fails to understand the bacteriological implication of a perioperative prophylaxis with gentamicin alone (Bair Hugger period) vs gentamicin plus teicoplasin. Dr. Samet did not address the bias in the use of no chlorohexidine alcohol skin prep during the Bair Hugger period vs the Hot Dog period during which time it was introduced. The many changes that occurred during the study essentially the SSI bundle – were also ignored by Dr. Samet, including case finding, preoperative skin cleansing, OR protocols, frequent team meetings and others.

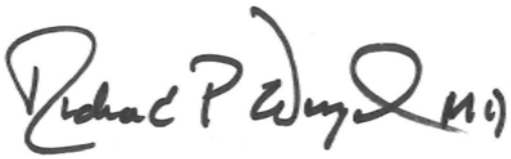
Dr. Samet's deposition is uncritical and wanting.

Of note, neither Dr. Jarvis nor Dr. Samet mentioned the five unpublished studies by Albrecht and others showing no bacteria observed in tests performed with the Bair Hugger device.

The overwhelming clinical data, national trends data during the Bair Hugger era and microbiological studies attest to the safety and benefits of the Bair Hugger.

To a reasonable degree of medical certainty, my opinion is that the Bair Hugger is not generally capable of causing a prosthetic joint infection. There is no valid scientific support for such a claim of any harm. Based on several lines of evidence, perioperative warming including warming with the Bair Hugger is a widely accepted infection control strategy.

Richard P. Wenzel, MD, MSc.



Date: 2 June 2017

Appendix:

Notes on Analogies of the Colonized Heater-Cooler Units

The plaintiffs allege that the Bair Hugger was analogous to the heater – cooler units, which have been linked to serious infections in patients after open heart surgery. The heater – cooler units used in cardiac surgery have been found to be contaminated with a single, very unusual organism – never before implicated in SSIs – *Mycobacterium chimaera*. This organism was not part of the normal patient microbiome and has been shown to have arrived on the apparatus from the manufacturer. An outbreak of *M. chimaera* infections has been demonstrated. No data support an outbreak of infections after use of the Bair Hugger. The species implicated are varied, and they are part of the microbiome of patients.

M. chimera is a slow-growing bacterium, a "distant cousin" of the organism causing tuberculosis. The infections typically are recognized many months after surgery. In part because mycobacteria divide slowly ~ every 24 hours. The reservoir (habitat) for *M. chimaera* is water. The organism was contaminated at the site of manufacturing before widespread distribution. The air from the HCU blows directly into the air in the operating room. The air in the Bair Hugger blows into the blanket and no one has shown that bacteria exit the blanket of the Bair Hugger.

The implicated heater –cooler units have a fan to cool the apparatus. The heater-cooler units have a large, open water tank, where the organism can be found. The fan directly blows onto the path of the surgical site, and *M. chimera* has been found in the air stream – the same species documented with a single fingerprint – as has been found on the machine and in patients. No airborne organism at the time of surgery with the Bair Hugger use has been linked to an organism found in the wound at surgery or subsequently in an infection, and recovered from the Bair Hugger.

Heater-cooler unit-related *M. chimaera* infections are totally different from those after use of Bair Hugger, which in fact has been shown to reduce infection rates.

Saxh et al. Prolonged outbreak of mycobacterium chimaera infection after open chest heart *Clin Infect Dis* 2015; 61:65-75. The author showed the same genus and species and fingerprint specimens from the water circuits of the heater, cooler unit and air samples when the device was in use, cardiac tissue specimens and blood cultures. This organism had previously never been known to cause post cardiac surgery infections, so a new epidemic was established.

Genetic analysis confirmed that many of the cases originated from source contamination at the Sorin 3T manufacturing plant. A spread within the hospital – a nosocomial link –was not established. Acherman Y et al. Prosthetic value endocarditis and bloodstream infection due to *mycobacteria chimera J Clin Micro* 2013; 51: 1769 – 73. Haller S et al. Contamination during production of heater – cooler units by mycobacterium chimera potential cause for invasive cardiovascular infections: results of an outbreak investigation in Germany. April 201 to February 2016. *Eurosurveillance* 2016:21.

Notes on Infecting Dose

For ethical reasons there are no studies showing the range of infecting doses of organisms that could cause an SSI after a joint replacement. For insight, the best data would come from animal studies of joint replacement – related infections.

Such models have been designed to create a reliable infection in a high proportion of animals to provide a reliable model of infections for study.

The models were not designed to identify the range of the infectious dose, but data from such animal models have been used to estimate the infecting dose.

Below are examples of some of the animal models used and the dose of organisms needed to cause infection. In each of these examples, *S. aureus* was the organism studied:

Notes on Animal Models – PJI-

Model/ref	No. Animals	Organism	Route of Infection	Inf Dose (cfu)
• English Short – Hair Rabbits Hip Durgery	125	*S. aureus*	IV	10^5
			Medullary Inoculation with prosthesis	<50
			Without prosthesis	10^4

Southwood
Br J bone Joint Sgy
1985; 67-B. 229-31

• New Zealand White Rabbits Knee Surgery Screw with polyethylene washer inserted	22	MRSA	Inject into knee	10^2, 10^3, 10^4 40% infection depending on dose; no change after 10^3

Craig
J Orthopedic Res
2005; 23:1100-1104

Model/ref	No. Animals	Organism	% Route Infection	Inf Dose
• New Zealand White Rabbits	10	*MRSA*	Injection into knee	10^5 - 10^8 cfu

Note: "With $5X10^4$ and $5X10^5$ cfu, only a few animals developed infection."
Belmatoug
J Infect Dis 1996; 174:414-7

• 12 week old mice Orthopedic k-wire placed into femur	Bioluminescent *S. aureus* injected into knee	$5x10^3$ or $5x10^4$ simulated acute infection; $5x10^2$ developed low grade infection, like a chronic infection

Bernthal **Note:** Some animals infected with only 500 cfus
Plos One 2010; 5: e 12580.doi:10.1371;

Journal.pone.0012580

Model	No. Animals	Organisms	Outcome
Sheep	10 5 -biofilm Infected 5 - No bacteria on film	MRSA	100% biofilm infected sheep became infected vs none of controls ~ 10 cfu/membrane

Williams DL
J Biomed Materials
Res 2010; 100: 1888-1900

Note: 1st model using biofilm organisms and not bacteria in solutions. The Goal was to simulate biofilm infection from a natural ecosystem contaminating a wound site after an open facture. MRSA, grown on a biofilm, was placed onto the tibia that had been stripped of periosteum and later covered with a stainless steel simulated fracture fixation plate.

Thus, the inherent flaws of animal models in predicting infectious doses in patients include the following:

1) No models use perioperative antibiotic prophylaxis, days of skin cleansing with antiseptic soap prior to surgery or use of topical nasal antibiotics to reduce the bioburden of the microbiome prior to surgery.

2) Almost all studies use virulent organisms, primarily *S. aureus* and not the relatively a virulent organism such as coagulase – negative staphylococcus or Gram negative rods. The infecting dose with less virulent organisms is likely to be greater than that with *S. aureus.*

3) The infecting methods in animal models include injecting bacteria directly into the prosthetic device or injecting a dose of bacteria directly into the bloodstream. Whereas the latter may simulate a perioperative bacteremia, the former does not happen in human surgery. Furthermore, no model has examined the airborne mode of infection.

It is generally thought that with a foreign body (joint prosthesis), the infecting dose of bacteria is less than that for surgery in which no foreign device is placed. The exact infecting dose range to infect 10% or 50% or more than 50% is unknown.

Addendum

- My CV and publications are attached as Exhibit A
- Materials used to inform my statements are listed in the body of my report. Others are attached as Exhibit B.
- My compensation is $600 per hour work and $700 per hour of testimony.
- I have not testified as an expert in the last four years.